BUSINESS IMPACT ANALYSIS
ESTABLISHMENT LICENSING/GMP COST RECOVERY

A report submitted to

DRUGS DIRECTORATE, HEALTH PROTECTION BRANCH,
HEALTH CANADA

by

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Executive Summary

This study, conducted on behalf of the Drugs Programme, examines industry reaction to new regulations designed to introduce an establishment licensing framework and uniform good manufacturing requirements for all drugs through addition of a new Division 1A and changes in Divisions 2, 3 and 4 of the Food and Drugs Regulations. This proposal replaces current regulatory requirements for manufacturers, and covers fabricators, packagers, labs, importers, distributors and wholesalers. The system takes a risk management approach to inspection and monitoring of the fabrication, packaging, testing, importation and distribution of drugs for sale in Canada. The study also examines industry reaction to a proposed schedule of fees that will accompany the new establishment licensing regime.

For the majority of enterprises involved in the study, the proposed regulations entail relatively little adjustment. Others will be subject to some additional requirements over the existing system, such as new requirements to adhere to GMP. For others, the regulations will be entirely new.

For those firms familiar with establishment licensing and GMP, concerns generally centred on harmonization with other jurisdictions and new requirements under the proposed regulations, such as Site Reference Files. Enterprises facing new or additional regulatory requirements under the new system were most concerned with potential costs of compliance, fees and interpretation of the regulatory requirements.

Based on our evaluation of both the quantitative and qualitative results captured by the BIT study, the most significant concerns were raised by small companies. For those companies in the BIT sample with annual sales of less than $2M, the proposed regulatory requirements and cost recovery are expected to impose costs of greater than 10% of total company sales. Cost recovery for these companies represented almost 3% of total sales.

Throughout the BIT responses and during follow up discussions with companies, questions were raised about the value of providing feedback to government on regulatory proposals. One company felt that the BIT response rate was low, and suggested that companies did not respond in greater numbers because they believed their input would not be used to effect any change in the course of events. This view is supported by a number of specific comments by companies who have participated in other BIT studies.

While it is not be reasonable to expect that the Drugs Programme can resolve all concerns raised in the BIT, the results clearly point to a number of key issues that need to be addressed prior to finalizing the EL/GMP and cost recovery regulations:

- Impact on small companies: Fee reductions on the basis of sales would help to alleviate the costs for small companies. As seen in the summary of costs, fees alone could represent an average of 3% of sales for companies with sales under $2M. Some relief from fees for these firms would help to reduce the negative effects on health food products, contract manufacturers and other sub-sectors of the industry.

- Low risk products: Some products within the proposed dosage form classes pose very little risk

to human health and safety (eg. Category 4 products). The regulations and cost recovery system should reflect that such low risk products require less effort on the part of the regulator to ensure public health and safety.

- Low risk manufacturers: Fees could be structured to recognize those firms where GMP requirements are consistently met. In comments on the draft report, the suggestion was made that a tiered fee system be implemented, whereby a base fee would be charged for inspections, with an additional variable fee component based on the actual time required to complete the inspection.

- Penalties for non-compliance. Companies generally felt that non-compliant companies should bear a greater share of the costs than under the current proposals. Fines or charges for the additional time required to inspect non-compliant companies would help to reduce subsidization of the enforcement workload by compliant companies.

Most of the other concerns raised in the BIT appear to be based on a questions of interpretation of the proposals or deal with issues outside the purview of the regulations. These issues should be addressed through ongoing communication and clarification by the Drugs Programme with their clients.

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Background

Drugs Directorate has developed a proposal to introduce an establishment licensing framework and uniform good manufacturing requirements for all drugs through addition of a new Division 1A and changes in Divisions 2, 3 and 4 of the Food and Drugs Regulations. This proposal replaces current regulatory requirements for manufacturers, and covers fabricators, packagers, labs, importers, distributors and wholesalers. The system takes a risk management approach to inspection and monitoring of the fabrication, packaging, testing, importation and distribution of drugs for sale in Canada. For some enterprises the regulations should entail relatively little adjustment. Others will be subject to some additional requirements over the existing system, such as new requirements to adhere to GMP. For others, the regulations will be entirely new.

This system will also entail cost recovery, the specifics of which are now under development.

Drugs Directorate advised industry that they intended to consult on these new proposals, and asked if the industry would like to participate in a Business Impact Test (BIT) study. BCI Regulatory Policy was contracted by the Drugs Programme to conduct a BIT survey and provide an analysis of the results.

Methodology

A model of questions based on the Business Impact Test was developed, specifically worded to pertain to establishment licensing and GMPs. The intention was to target questions to the issue at hand, eliminating those BIT questions that could be considered irrelevant for EL/GMP regulations. The questionnaire was designed to be shorter and easier for respondents to understand, collecting more focussed responses from participants. Respondents were also asked to complete a fee calculation form as part of their assessment.

On August 16, a brief information session was given to members of the industry to introduce the BIT survey and distribute survey packages to participants. Forty packages were distributed to individual companies and business associations at the August 16 meeting. Participants were asked to return their responses by September 13, 1996.

By September 26, 26 responses had been received (65% of the 40 distributed). Each response was reviewed for completeness and some follow up was done with individual respondents where clarification was required.

On October 4, a draft report was sent to all BIT respondents and associations for comment. Comments from three associations and 3 companies were received, and are reflected in this final report.

Summary Information on the BIT Sample of Companies

Total number of responses: 26

Number of corporate entities represented in sample: 27
Number of associations: 1

By Type of Activity:

Manufacturer (fabricator)	12
Packager	8
Importer	10
Distributor	6
Wholesaler	2
Testing laboratory	4

By type of business:

Pharmaceuticals	15
Radiopharmaceuticals	0
Narcotics	5
Veterinary Drugs	3
Biologicals	3

Total Sales reported: $2.34B

By number of people employed (not indicated by all respondents):

Not indicated:	5	20%
Less than 50:	2	8%
51 - 100:	7	28%
101 - 500:	4	16%
501 - 1000:	4	16%
More than 1000:	3	12%

Initial Reaction

Responses indicated that the rationale for the new system had been clearly articulated in the documentation and via the August workshop. While 80% of respondents indicated that rationale for EL and GMP system had been accurately described, a number also indicated some concern. The chief concerns were that cost recovery appeared to be the principal driver behind the new system and the rationale for licensing testing laboratories

Two-thirds of respondents felt they understood the requirements under the new EL regime for their companies, with the following issues needing clarification:

- license applications, amendments and renewals
- handling consignment warehouses
- Guidelines for site reference files
- Information on the PIC form
- Progress on MRAs

The new EL regime will entail additional site license requirements for 65% of respondents, and both GMP and site license requirements for 32%. It was indicated that GMPs have the greatest impact for companies in terms of organization and cost, and site licenses may be viewed as an effective management tool by industry. Of concern from a public policy standpoint was recognition that the new regime may pose an effective barrier to new entrants.

60% of participants felt the EL regime would have a significant impact on their businesses. Harmonized GMPs was a particular concern raised by importers and those with foreign manufacturing sites. Custom manufacturers were most concerned about the impact on their business, and their was almost unanimous agreement that for those companies facing new requirements under the EL regime, the costs of attaining compliance was the key issue.

Affect on Activities within Companies

The impacts on company activities generally related to the size and scope of operations, and the extent to which the new EL regime would entail additional or entirely new requirements for a company. On average, about 50% of the responses indicated "no impact" for each business activity. The main areas that would be negatively affected were administration, budgeting, finance, and human resources. Positive effects were mainly in the areas of sales, supply management, marketing and client services. The following comment provides an excellent summation of how the EL regime may affect individual activities within companies:

The proposed fees will be factored into the annual budget and are paid out of cash flow thus having a minor negative effect on budgeting. Until the value of the establishment license is demonstrated to be greater than the value of the present GMP compliance inspection process, the fee will be seen as a subtle form of taxation. The effect on financing is short term and a consequence of repatriating manufacturing activities from contract manufacturers who are unable to survive the costs of licensing implementation and compliance with the new GMP guidelines.. The assessment of a negative impact on

supply management is based on the assumption that smaller suppliers will be driven from the market by the costs of establishment licensing and compliance with the new GMP regulations and guidelines. The forced consolidation of small specialty suppliers will reduce competition in this area and conceivably result in higher costs. This affect is compounded at the contract manufacturer level by the costs they will incur in complying with the new GMP guideline particularly the area of validation. The positive effects are predominantly felt in the areas of sales and marketing. Their value is based on the assumption that a license issued by Health Canada will confer a competitive advantage in international circles. Historically, jurisdictions are extremely hesitant to recognize the value of such a license. As an example, Canada does not accept the GMP certificates issued by European countries as evidence of compliance with GMPs without a thorough review of written inspection data. Conversely, the United States will not accept other jurisdiction's assurances and will conduct independent inspections. The Drugs Directorate's efforts to negotiate MRA and MOU agreements are recognized, however, until this lengthy process is accomplished with major trading partners, the value of a license internationally is extremely limited

Impact by Business Type and Size

Throughout the comments received from BIT respondents, the effect of the new EL/GMP regime varied by type and size of business.

Small Business: Since fees do not relate to sales, but rather to the cost of inspections based on type and scope of the facility, small firms found the costs to be a much more significant portion of their business than larger firms.

(T)his fee proposal (as was the case with phase II) puts a much greater burden on smaller companies than on larger ones. Already, Canadian manufacturing operations are perceived as being much less (-20%) competitive than their US counterparts.... within our group, these proposals will have detrimental effects (even prohibitive) on some members.

Because of the size of our company and the type of business, we are involved, we will probably have to pay fees equal to much larger organization with may be 20 times less gross sales.

Veterinary Drugs: Veterinary drug manufacturers completing the survey consistently expressed concerns about the illegal importation and use of active ingredients by veterinarians, pharmacists, and producers. Veterinary drug manufacturers indicated that the additional costs of licensing and GMP further reduces their ability to compete with illegal imports:

The US is about to undertake consultations to develop separate veterinary drug guidelines. Already FDA regulations clearly place Canada at a disadvantage in terms of control over illegal import and use of active pharmaceutical ingredients (API's).

Separate guidelines for the veterinary field are an absolute must. The Food & Drug Act must also recognize active pharmaceutical ingredients in addition to drugs in dosage form.

Unless separate veterinary guidelines are annexed to the GMP guidelines, we will have to consider a close down with a loss of up to 50 permanent jobs.

Natural Health Products: Specific concerns were raised in the homeopathic and herbal sector about the potential effect of EL/GMP requirements and user fees on their ability to respond quickly to specialized, niche product demands from customers.

***Contract Manufacturers*:** Contract manufacturers and companies who use contract suppliers feared the effect of compliance costs on this sector of the industry. A number of firms indicated that manufacturing would likely have to be "repatriated", as contract manufacturers are expected to become fewer in number and more expensive.

The forced consolidation of small specialty suppliers will reduce competition in this area and conceivably result in higher costs. This affect is compounded at the contract manufacturer level by the costs they will incur in complying with the new GMP guideline particularly the area of validation.

Impacts on products and markets

Companies almost unanimously felt that the quality and recognition or acceptance of their products in the market place would not be affected by the EL regime. While companies did not indicate a large impact on product prices in a subsequent question, some companies, especially those involved in the nutritional supplements business, indicated that acceptance of their products might be negatively affected by price increases that would result from EL and GMP costs and fees. One company indicated that a heightened standing in the market that could result from El and GMP compliance would accrue only to the extent that compliance was assured for all competitors in the market. Overall, it does not appear that companies view compliance with EL and GMP requirements to be an effective way to differentiate their products from competitors on a non-price basis.

Two thirds of respondents did not foresee any impact on their ability to access either domestic or foreign markets. Of those companies who did see an impact on market access, a greater number believed that benefit would occur in accessing foreign markets than domestic markets. Concerns about negative impacts on either domestic or foreign market access related to:

- custom manufacturers
- marginally profitable products
- potential delays in license process
- impact of fees on price competitiveness of Can products in foreign markets

Thirty-five percent of respondents indicated a concern about the impact of the new regime on timing to market:

Companies in a start-up or growth phase may be negatively affected. When a decision is made to add a new dosage form onto the license, there would be a delay from the time that the

company is ready to manufacture until the license is approved.[1] This would be more critical for contract manufacturing companies. Potential manufacturing sites (particularly non Canadian) may not have obtained EL or have outstanding issues which need to be resolved.

Site Reference File preparation for foreign sites, time to develop/educate the site regarding requirements and to prepare and maintain the new documentation requirements will add extra time to the process for market introduction.[2]

The time that it takes to certify a new dosage form (class) may negatively impact our ability to get new products to market. This is dependant on the delay from the time of application to the approval of certification.

The potential effect of the new regime on the ability to meet customer requirements was viewed to be negative by 28% of respondents and positive by 16%.

Impact on General Business Conditions

Less than one half of respondents anticipate a negative affect on their relationships with other businesses, and only 12% thought their relationships with other organizations might also suffer. While the new regime was seen to potentially stabilize business for compliant contract manufacturers, there was also a concern that the costs of compliance may skew the contract manufacturing market to larger and fewer firms:

The existence of a license would not remove our corporate responsibility to qualify and audit firms we choose to source products and expertise from. In the longer term, the licensing proposal has the potential to skew the market towards larger firms who are more capable to finance and administer a mandatory license program.

Operational Changes for Companies

While 40% of respondents indicated that there would be no impact on personnel, other respondents felt that the proposed regulations could require them to hire, redeploy or in some cases dismiss personnel:

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[1] To clarify this point, the regulations will require license amendments when a company moves into a different dosage form CLASS. This means if a site is already licensed for tablets then the company can add as many new tablet products to the manufacturing site as they need. If they are licensed to make solutions but then want to make tablets the site license must be amended to include the new dosage form class.

[2] There appears to be a divergence of opinion about the burden of preparing a Site Reference File. The Drugs Programme assumes that companies should already have the required SRF information on hand, and that the SRF provides a format for that information to increase inspection efficiency. However, concerns are raised throughout the BIT commentary about the potential burden of preparing an SRF and little credence is given to the role of SRFs in improving inspection efficiency.

There would likely be a modest increase in the number of employees responsible for maintaining the dialogue with the HPB and compiling documents to satisfy the site reference file requirement. The added regulatory burden of compiling and maintaining the site reference file cannot be measured accurately but is likely to be significant. The data requirements for the site master file have not been adequately discussed and, while the assertion that the site reference file will be brief is recognized, past practice within a bureaucracy has demonstrated that the additional regulatory requirements never lessen a paper burden. Estimates of the work required to compile and maintain the proposed site reference file cannot be undertaken without concrete guidance. This added workload would be undertaken in addition to other regulatory duties and preparation of submissions for approval.

Redeploy: Personnel may have to redeployed to administer / conduct foreign licensing and GMP inspection programs. Longer term, the potential increase in expenses may eliminate our ability to hire additional staff.

Hire: This would probably entail a need to higher more QC/QA personnel.

Current operating procedures will be affected for 80% of respondents; about one third expect major or prohibitive impacts. The major affect appear to be in preparing site reference files. However, in some cases major impacts were viewed in a positive light:

Major: Quality Assurance will be more focussed on validation/contractual agreements, with foreign fabricators/packagers, and systems to ensure that only Canadian acceptable product crosses the border and that controls over distribution are adequate to Canadian needs. Our focus will be shifted to proactive Q.A. activities prior to shipment to Canada, and less toward the reactive repeat testing currently required post shipment.

Minor: Increased administrative costs due to licensing fees will increase the relative cost of manufacturing services, decreasing the amount of work conducted. Rate of growth will be slower, affecting plant capacity and utilization projections.

Change control process would be affected if it must include license amendments and in some cases approval from HPB prior to implementation.
Site Master File preparation and maintenance will be a new process.
There will need to be an increased focus on supplier/contractor GMP audits/contractual agreements.
Responsibility for maintenance of license and payment of fees must be established internally. Budgeting procedures will be affected.

Facilities and productive capacity did not appear to be greatly affected by the regulations, with the most severe adjustment expected for small contract manufacturers.

Impact on Business Investment and Growth

Forty percent of respondents believe that product development will be affected by the new regulations, mainly due to the effect on suppliers and the license implications of adding a new dosage form class. One third expect a negative impact on research and development due to the effect of fees on overall funds available for such work.

Almost one half believe that expansion would not be limited by the new regulations. On the down side, companies raised concerns about mounting administrative burden in Canada and the impact on their ability to attract investment to expand, divest or restructure:

On a global scale, our corporation will continue to develop a negative feeling about production from a Canadian facility if our administrative costs continue to increase. The likelihood of a plant closure continues to increase. This has already occurred in our associated facility in (city).

The regulatory climate in Canada has been viewed positively by investors. Changes to this climate may cause Canada to lose this advantage. May affect specific construction plans of new facilities since fees are partly based on number of buildings.

Negatively affect our ability to compete within out company worldwide as a manufacturer. The additional requirements and associated costs along with other aspects of cost recovery may lead to a decision by our parent company to reduce its investment in Canada and source products for Canada from other countries.

Cost Recovery

Most respondents felt that the fee calculation form helped them to understand and calculate their fees. A number of technical problems were reported concerning the Excel version of the spreadsheet which may skew the results[3] to this question. Clarification appears to be needed in the following areas:

It is not clear how to interpret "# Drug Categories" or "Total Dosage Increment Fee". This would be almost impossible to understand if English were a second language. The existing form needs to be edited to clarify definitions of "building". A guidance document is required particularly for the "GMP inspection component" in blocks 1 &2. Tables should be provided indicating drug category and dosage class (as in Table 1 August Consultation document Appendix E)

My packaging operation in (city) (it labels the filled imported packages with Canadian labels) is also the importer/distributor for our ethical drugs. I believe the forms have caused me to

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[3] BCI Regulatory Policy converted the Lotus version of the fee calculation form developed by Drugs Programme to an Excel version to provide respondents with a choice of applications. The errors occurred during the conversion, not with the original product developed by DP.

double count. For example the lab looks after both the filled unlabelled imports and the final labelled packages. It would have been more accurate to complete the Importer section and just make a small base charge for inspection of the local packaging operation.

It appear that the potential impact on the number of sites and the types of products offered for sale will not be significantly affected by the fees. Product price increases and corresponding drop in sales revenue are expected by a third of the respondents. On average, impacts on prices and sales were not anticipated to be significant. However, contract manufacturers and those firms selling "non-traditional" therapies felt the effect on prices and sales could be dramatic. These results are mirrored in terms of profitability and cash flow.

While not directly linked to EL and GMP fees, the question of the cumulative burden on cost recovery drew a lot of comment. Companies felt that the total bill for the three phases of the Drug Programmes' cost recovery plan had become significant for many companies, often representing in excess of 1% of total sales.

Design Issues

In examining the specific elements of the EL and cost recovery regime, companies were most concerned about issues of clarity and fairness. While the Drugs Programme should examine each concern raised and attempt to provide clarification, the following recurring issues should be the focus of their efforts to revise and explain their proposal:

- instructions on fee calculation
- compliant manufacturers are subsidizing non-compliant
- guidelines for SRF
- fees owing for a fabricator who is also importing
- do the regulations now allow direct shipment to Can customer from US site
- exact options to verify compliance of foreign sites

Concerns regarding equity seem to relate to the need for the Drugs Programme to target its efforts in the areas of greatest risk and a perception that there may be double-dipping in the fee structure, as articulated in the following comments:

If the foreign fabricator holds Canadian license then the importer should not have to pay an additional Foreign GMP Inspection fee or Analysis Fee: then the requirement to pay these under both Fabricator and Importer constitutes "double dipping". This is especially true with Biologics Fabricators which are required to be licensed. An option should be identified on the form if: I) The foreign fabricator holds a Canadian license then the importer should pay an Analysis Fee or Foreign GMP inspection fee; ii) if the importer is a Canadian licensed Fabricator, then they should not be required to pay an additional domestic GMP inspection Fee under Block 2. To do so would constitute a double payment.

Cost recovery in general should be based on the relative amount of available resources the HPB must dedicate to a particular segment of the industry. The high degree of product safety

and lack of technical complexity associated with the nutritional supplements segment makes it a very low risk and resource drain on the HPB. Therefore, we should not have to pay for the same degree of regulatory control that is required by allopathic OTC products. There should be a sliding scale of costs based on risk (greater than in the proposed program). Also, fees should be based on the effort required by HPB to perform an audit. As with annual product licensing, low product or category sales should result in a dramatically lower fee. Also, if a company is both a manufacturer and an importer, they are being charged twice for basic GMP and analytical requirements - this is not fair. This needs to be adjusted to a single charge.

It appears that a domestic manufacturer would be disadvantaged from a fee standpoint if an importer has supplier's assessed through an MOU or MRA (ie the fee for this type of assessment is less than the fee paid if manufactured in Canada). This is of concern since it does not promote domestic manufacturing and the subsequent positive impacts of this on the Canadian economy.

It appears that a domestic manufacturer would also be disadvantaged from a licensing application and maintenance standpoint in that changes must be sent to HPB for possible approval. This does not appear to be the case if the manufacturing is done outside of the country.

Regarding the statement that licensing will provide a "level playing field", compliance and enforcement focus will be based upon risk assessment and therefore it is not a truly level playing field, ie more latitude will be given to sectors deemed to be less of a health risk

Concern about the cost of the new regime relate to both the structure of the EL and GMP regulations and the application of the fees:

An importer receiving several drug classes from a few plants will pay substantially less than an importer receiving the same products from many plants because of the $1250 flat rate for each foreign inspection report review. The cost of reviewing each inspection report seems excessive and there should be a reasonable upper limit or declining scale for report and reviewing from multi-site importers. As an importer using many sites my fees for reviewing foreign reports are approaching 70% of my total importer fees.

As mentioned above, the cost for the nutritional supplement segment of the industry is too high. Costs should be based on risk and relative resource requirements. As well, there should be a sliding scale to grade the fee based on category or product sales. Also, if a company is both a manufacturer and an importer, they are being charged twice for basic GMP and analytical requirements - this is not fair. This needs to be adjusted to a single charge. The charge for inspection fees to an importer from a MRA country is too high. The amount of HPB inspector effort to review compliance of a foreign MRA government inspection is very small - not worth the $1250 being charged.

A recurring comment from the veterinary drug sector is their prime concern for illegal importation of veterinary drugs. These companies perceive little benefit to the proposed system

and paying the associated fees when they do not have confidence in the government's ability to prevent non-compliant, and therefore lower cost product from entering the Canadian marketplace.

Duplication

Comments about duplication at the federal and provincial level focus on fees, and appear to reflect an increasing level of frustration of firms with the cumulative impact of cost recovery initiatives by both levels of government. In terms of duplication with other jurisdictions, respondents key concerns focus on harmonization with FDA requirements:

FDA continues to do pre-approval inspections (PAI) for products manufactured in the US for the Canadian market. We must therefore prepare for two kinds of inspections namely HPB/GMP and FDA PAI. The effort spent amounts to the possibility of several weeks to months of government inspection. The effort is labour intensive taking away the ability to focus on product development and production.

FDA GMP's and HPB GMP's are not absolutely harmonized regarding some of the details either as defined by the regulations or by respective administrative practice.

US requirements for manufacturing drug products do not always agree with Canadian requirements. Foreign (US) sites are forced to do additional work (eg. extensive raw material testing) in order to comply with Canadian GMP standards.
Also, Canadian GMPs require duplicate testing after receiving a drug product into Canada.

Bilateral agreements between Canada and certain other countries should imply that the bottom line acceptance of a facility by another jurisdiction should be taken at face value. We do not see any merit in HPB reviewing those reports at a an extra annual cost to the manufacturer. It will be a duplication.

Costs and Benefits

The following table summarizes the initial and ongoing costs anticipated by companies in the study. Fees represent the largest proportion of anticipated costs, 37% of initial costs rising to 52% of the ongoing costs of the new EL regime for companies. Administrative, operating and lost sales revenue are the other main areas of cost of compliance for companies.

Summary of Costs for All Respondents

	Initial Cost ($000)			Ongoing Annual Cost ($000)		
	Total	Average	% Tot.	Total	Average	% Tot.
Administrative costs	281	14	25%	201	10	17.7
Operating costs	212	11	19%	221	11	19%
Capital costs	100	5	8.9%	0	0	0%
Fees	414	21	37%	592	29.6	52%
Sales Revenue	100	5	8.9%	218	10.9	19%
Total	1,128	56		1,138	57	

Total costs appear to average around $57,000 for companies, which vary substantially based on the number of sites, dosage forms, etc. The incremental costs are greater for those companies with no previous exposure to site licensing or GMP requirements. The impact of these costs is, of course, of greatest concern to companies with low levels of sales.

Summary of Annual Costs by Sales Range

	Total Sales ($M)	Average Sales ($000)	Total Costs ($000)	Costs as a % of Sales	Total Fees ($000)	Fees as a % of Sales
Less Than $2M	$2.6	$870	$269	10.3%	$76	2.9%
$2M to $100M	$418	$34,800	$525	0.13%	$280	0.07%
More than $100M	$1,927	$241,000	$325	0.02%	$216	0.01%
All	$2,347	$102,000	$1,138	0.05%	$592	0.03%

This table indicates that the costs of the new EL/GMP system and cost recovery hits hardest on those enterprises with relatively low sales. Based on the estimates provided in the BIT, companies with annual sales of less than $2M expect costs of implementation to exceed 10% of their sales, and fees to account for almost 3% of sales. The most significant cost reported by these companies was potential cost of lost sales, which accounted for 37% of the overall costs reported.

Personnel Costs

Impacts on personnel costs are expected to be minimal, with a number of companies indicating that anticipated workload increases would be met within existing resource levels. However, most companies in the BIT sample indicated that it was difficult to provide an estimate prior to

actual implementation of the new El and GMP requirements. The comments below provide an overview of potential effect of the proposal on personnel costs:

An estimated 3 additional full time employee would be required should (this company) need to repatriate manufacturing capacity. The additional workload associated with the preparation and maintenance of the site reference files will be integrated within the present workload.

Preparation of establishment licence will take:
- l fulltime regulatory person to prepare forms: 10 working days
- 1 fulltime administrative person: 5 working days
- 1 manager to prepare budget: 2 working days
- 1 finance person to review: 1 working day
- 1 material management person: 2 working days
to confirm site detail

Impact on Competitiveness

Respondents felt that their ability to compete outside of Canada (48%) would be more greatly affected by the EL regulations than their ability to compete domestically (36%). Within Canada, the negative impact on ability to compete related to the proportionately larger burden imposed on small firms. Ability to compete in foreign markets is expected to affected mainly by lack of MRAs and MOUs with the US, EU and Pacific rim countries, and increased cost of Canadian products.

In Canada less, because we are competing with large companies who have one plant which manufacture all they do, and make huge runs. As a niche seller, we don't have the large runs to amortize all these huge costs over. In other countries, they have their own GMP's which may or may not match Canada's. Also their we are competing with huge run manufacturers the same way. Your are treating us as "pharmaceutical" manufacturers when in fact we are not!

More in Canada: Within Canada, (this company) is in better compliance with required GMP Guidelines than the majority of our competition. Therefore, these new requirements will affect others more than us. This new initiative will go a long way in enforcing a "level playing field" that should prove beneficial to (this company). Less in other countries: Externally, the cost of Canadian manufactured products will be relatively higher than other countries due to the increasing volume of additional Canadian taxes we are forced to pay.

The ability to import product from foreign sources is now limited. Previously Canadian industry was able to obtain product from any source meeting. Canadian GMP based on either a Plant Mater File, corporate audit report, Canadian GMP foreign inspection or a foreign GMP report. This puts the liability of importing a product appropriately in industry hands and allows greater access to foreign sources. The current plan provides access to a limited number of countries with which we have a MOU to obtain inspection

reports. The plan for recognition of foreign GMP through MRAs with the US, EU and Japan and possible agreements with NAFTA and Asia Pacific Rim is not in place. It is clear that EL under the current plans is not sufficiently developed to make it useful to industry. Once MRAs are in place however, we will be in a better position to compete for manufacture for world markets.

For local needs our access to contract laboratories, wholesalers and distributors will be limited to those willing and able to pay the fee. The risk of closing smaller Canadian business is increased. The EL fees appear higher in Canada than other countries and could limit continued manufacture in Canada.

Less: Because of the size of our company and the type of business, we are involved in (Custom manufacturer), we will probably have to pay fees equal to much larger organization with may be 20 times less gross sales.

Summary Comments

Half of the respondents believed that the new EL regime would achieve Health Canada's objective of providing a uniform, consistent and risk based approach to establishment licensing in Canada. Issues of relative risk and focussing on non-compliant firms was the focus of most comments:

The Food and Drugs Act and Regulations were conceived in an era of absolute risk avoidance. However, current risk management practices necessitate selectively surveilling and enforcing compliance where the risks are the greatest. The present Act does not accommodate these objectives easily. The efforts of the Drugs Directorate to adapt the Food and Drugs Act and Regulations to address the current health and fiscal environments are analogous with conducting delicate surgery with a truncheon. Compliant manufacturers exercise good manufacturing practices, regardless of legislation, to minimize product liability and to enhance quality as a competitive tool. Concern with noncompliance is less immediate to a manufacturer than concern with potential liability and loss of profitability. Literature suggests that the frequency of inspection is the greatest motivator for compliance amongst noncompliant firms and is only effective in accomplishing compliance if the inspection frequency does not exceed 3 years. Manufactures with a history of compliance stay compliant without intensive government surveillance because integrating GMPs in the culture of the organization is the most cost effective means of minimizing product liability and maintaining product quality and consistency. Company vitality and profitability stems from being consistently able to enter markets with high quality products manufactured under consistent conditions. The most effective way to manage risks associated with GMP noncompliant firms is through more intensive market surveillance not, through regularly and habitually inspecting compliant firms. The value of a license is minimal to compliant firms. The international value of the license as currency is constrained by divergent political agendas and the absence of broad acceptance by our trading partners. The Drugs Directorate Inspection Strategy may be better served by developing mechanisms to defer the monitoring of compliant firms to a separate body and concentrating on those firms who pose a greater risk to the public. Serious consideration

should also be given to rewriting the Act and Regulations to reflect HC objectives amid current realities.

Category IV drugs should have been charged in a lesser way than other OTC's to reflect substantially lower risk. Audits involving many sites with few products each provide a much more thorough (and expensive) review and greater benefit to risk reduction than audits involving few sites with many products and product types each.

Greater harmonization was supported by the majority of respondents, although specific ideas about how to achieve greater levels of harmonization were scant.

The HPB concept of GMP and the FDA concept of GMP are very similar differing only in a few details. Yet the devil is in the detail. When a company tries to harmonize and satisfy both, it must either take the most conservative course (with cost implications to all North America) or run the risks associated with the complexities of running two systems. Canada should fully and unconditionally accept US cGMP's from US plants. US should fully and unconditionally accept Canadian GMP's from Canadian plants.

The Site Reference File (SRF) is another Canada specific document. The information requirements should be harmonized with countries with which we achieve a MRA. The work of preparing such a document for every building we use is an additional burden to industry. We believe the SMF will not reduce the GMP inspection. The level of detail (which has not been clearly defined) is less than the current Plant Master File.

If HPB will accept the GMP reports of other countries without wasting further time and effort on reviewing them annually at our expense, harmonization will be useful. But that does seem to be the proposed intent.

Aiternatives

Fifty percent of companies believed that improvements could be made to the current proposal, and offered a number of specific ideas with some specific examples to emulate:

For firms with a history of compliance with the GMP requirements the Drugs Directorate should consider accepting the results of corporate inspections. Corporate inspectors could be accredited by Health Canada and requirements to maintain accreditation developed and written into regulation. The Drugs Directorate could then concentrate on delinquent or start-up firms. The approach of involving industry as inspectors for the purpose of achieving federal objectives has been instituted by the federal regulators responsible for weights and measures and operated with success. The authority to designate inspectors is vested with the Minister of Health and not limited to federal employees

Full blanket recognition of US cGMP's, and others as appropriate, consistent with the full blanket approach of Canadian F&D Act Schedule "B" acceptance of USP & various other pharmacopoeia or child resistant packaging standards similar to Schedule 800 of Canada

Gazette Part 1 June 10, 1995. It is noted that the US cGMP's already appear in the USP which is recognized in Schedule B to the Food and Drugs Act.

Separate categories (even if within the drugs directorate) for nutritional supplements would provide for a more equitable allocation of resources and, therefore, fees to be recovered. Another way to fairly allocate fees to be recovered, based on relative risk (and therefore the amount of government resources required) could be to develop a compliance rating system. This way companies could be graded according to their peers in their specific market segment, eg. nutritional supplement manufacturers. Fees could be decreased based on good performance (similar to car insurance discounts). Fees should be based on relative level of required government resources. Clearly, companies requiring assistance in achieving GMP compliance, or marketing products in higher risk categories, will require more government resources - they should pay more than low risk, high compliance companies.

In summary, the key concerns raised by respondents were:

- Concern that EL and GMP regulations do not focus on relative risk of products or non-compliant companies
- Impact on small, niche companies
- Impact on natural health products and contract manufacturers
- Impact on investment
- MRAs and MOUs with major trading partners
- Impact on marketplace consolidation
- Impact on manufacturers who fabricate and import drug
- Need to define a phase-in period
- Role of self-inspections and internal audit reports in foreign site compliance
- Whether Site Reference Files mandatory
- SRF guidelines
- How non-licensed companies will be dealt with

Conclusions and Recommendations

As discussed throughout this study, most companies indicate that the proposed regulations will entail relatively little adjustment. For those firms familiar with establishment licensing and GMP, concerns generally centred on harmonization with other jurisdictions and new requirements under the proposed regulations, such as Site Reference Files.

Enterprises facing new or additional regulatory requirements under the new system were most concerned with potential costs of compliance, fees and interpretation of the regulatory requirements.

In a number of instances, the issues raised by industry can be addressed through continuing communication and clarification by the Drugs Programme with their clients. In particular, more

clarification and information is needed with regard to the MOU and MRA process, inspections of foreign manufacturing sites, and fees for companies who both fabricate and import. Also, while there appears to be a divergence of opinion as to whether the illegal importation of veterinary drugs issue can be addressed as part of this regulatory initiative, this issue needs to be resolved with the veterinary drug industry by the Food Directorate and the Drugs Programme within Health Canada.

Issues for Resolution

Based on our evaluation of both the quantitative and qualitative results captured by the BIT study, there are a number of substantive issues that should be addressed prior to finalizing the EL/GMP and cost recovery regulations:

- Impact on small companies: Fee reductions on the basis of sales would help to alleviate the costs for small companies. As seen in the summary of costs, fees alone could represent an average of 3% of sales for companies with sales under $2M. Some relief from fees for these firms would help to reduce the negative effects on health feed products and contract manufacturers.

- Low risk products: Some products within the proposed dosage form classes pose very little risk to human health and safety (eg. Category 4 products). The regulations and cost recovery system should reflect that such low risk products require less effort on the part of the regulator to ensure public health and safety.

- Low risk manufacturers: Fees could be structured to recognize those firms where GMP requirements are consistently met. In comments on the draft report, the suggestion was made that a tiered fee system be implemented, whereby a base fee would be charged for inspections, with an additional variable fee component based on the actual time required to complete the inspection.

- Penalties for non-compliance. Companies generally felt that non-compliant companies should bear a greater share of the costs than under the current proposals. Fines or charges for the additional time required to inspect non-compliant companies would help to reduce subsidization of the enforcement workload by compliant companies.

- Consolidation of dosage form classes: It appears that a simplification of the dosage form classes is needed. If dosage form classes are based on differences in manufacturing processes, then it appears that a further consolidation of dosage forms (i.e. grouping tablets, capsules and powders together) is possible.

- Fee forms: Some minor clarifications to fee form are required. While very few comments were received about the fee form, some parts of the forms were consistently misinterpreted. These areas should clarified with improved wording, explanation and examples.

COMPANY SURVEY RESPONSES

Based on your reading of the discussion document:

Has the rationale for implementing a new establishment licensing regime been described accurately in the documentation you have received? Yes__20_ No__5___

3. You are saying that the rationale is to ultimately benefit the end user. We in the Natural products industry have products which are not covered by Insurance Drug Plans, and this all means increased costs to the end user. As far as I can see, the rationale is to collect money, with nothing in return. The rationale for implementing Cost Recovery (which includes Establishment Licensing) was given to Health Canada by the Treasury Board; "If a subset of the population benefits from a government department, then their should be some applicable user fee". Canadian health care costs contribute greatly to the National Deficit and ultimately the public. The subset of the population (end user - public) will only realize an increase in the cost of drugs. We solely import nonprescription drugs, the majority of which are not covered by Insurance Drug Plans. This scenario will create one of increased costs which will be handed down to the end user. In a competitive market this will be a burden on business (small companies will not survive) and the public pays for it. Perhaps the public should be consulted.

6. Yes: The rationale has been described accurately however, the rationale has been hidden in the cost recovery aspects and rationale found in the document

9. Yes: It totally fails to address the issue of illegal importation and subsequent use of pharmacological active ingredients.

10. Yes: These changes are intended to streamline varying levels of licensing and inspection activities for all products listed in Schedules A to D of the Food and Drug Regulation as well as Compliance under one set of GMP regulations as outlined in Division 2 of the Food and Drug Regulations. Based on attendance at the Drugs Programme workshop, it was apparent that fees for establishment licensing are required to replace funds to the Drugs Directorate Board due to Treasure board Policy cuts. This part of the rationale was not clearly discussed in the discussion document.

19. No: There seems to be a lack of information related to the application of licensing and how it will benefit the industry members. The sole rationale expressed is the cost recovery of $8 MM annually, which seems to be a partial benefit/reasoning.

23: Yes: The rationale has been explained clearly.

24: No: References to testing laboratories is brief and not very informative. No adequate reason explaining why testing laboratories should be licensed has been given - the purpose of this remains unclear.

25. No: The rationale provided indicates that the efficiency of compliance and uniform application of GMPs are the reasons for this. The HPB currently has the same mandate and the same regulatory authority to do the same thing as proposed. If it was not done in the past, how can it be accomplished with the new proposals. The real reason appears to be that the fees will be charged for providing same service

26. Yes: In terms of rationale, yes. In terms of its application to the veterinary field, no.

Do you understand what the requirements of the new establishment licensing regime will be for your business? Yes__15__ No__8___

1. To a great extent yes. One of the difficulties results in assessing the multiplicity of corporate structures under the same management and under the same roof.

6. No The document does not contain sufficient details on license applications and license amendments. There is no information provided on time frames required to have license amendments approved.

10. Partially: It is unclear how a fabricator will submit amendments/changes to existing licenses. How will Facility renewals be handled? Details of what will be required for submissions are not given.

11. No: I am not sure if three consignment warehouses should have somehow been included in the fee calculation. I am not clear on whether to included fees for review of foreign audit reports because I am unclear on the importance of obtaining "Authorized Foreign Facility Status".

14. Yes: 1. Requirements for the preparation of a Site Reference File require Guidelines. As presented there is insufficient explanation to develop.

2. Examples provided are for simple businesses and add to confusion around issues of sites and buildings in the calculation of applicable fees.

15. No: l. The Mutual Recognition Agreement (MRA) to accept inspection reports from EU, US and Japan is not in place. No agreement with ASIA Pacific Economic Community (APEC) has been reached with respect to recognizing GMPs. If establishment licences (EL) are implemented, industry is limited to importing products where we have a Memorandum of Understanding (MOU) to access foreign inspection reports or the HPB must inspect foreign sites.
2. The fee schedule requires further clarification.
3. The site Master File (SMF) requirements are not adequately described.

17. Yes: I have a good general understanding, however the specific requirements of the submission for a licensing establishment and the time required between application and licensing are missing.

18. The broad requirements are clear, however the mechanics of submission for license, implementation details and guidance on preparation of Site Master Files is still required.

19. No. This is the most incomplete part of the document: the requirements of the newly established regime. For manufacturers currently involved with the GMP's it is probably clearer, but for wholesalers there is no clear indication other than the fact that there will be a licensing process which may look like the Pharmaceutical International Convention Form (PIC). However, this form and confirmation of the process is not available. Following the GMP may be unclear for wholesalers as we carry many different products in a variety of storage environments which may or may not be under the jurisdiction of the new regulations. The ability to control and track lots/batches is mentioned but no detail is provided as to what information will be mandatory.

It is unclear as to what a site master file, or site reference file are, yet the PIC format is suggested.

Procedures and qualified personnel are referred to in the discussion document but not defined therefore the specific requirements and impact upon us is unknown.

20. No: We need more information with respect to:
- On site reference file
- Timing for role out and reference files.
- Information on renewal.

21. No: The information available leaves us with many questions on the application of the fees. Also, we believe that it is open to interpretation.

23. No: Not every aspect has been explained clearly enough (fee matrix is not totally clear and neither is the criteria for establishing compliance of foreign sites). Our current assumption is that internal audit reports showing compliance of foreign sites are also an acceptable way of establishing compliance.

24. No: Definitely not. These are not outlined anywhere. We can speculate and we have ideas of our own about what the expectations may be but we do not have "guidelines" that we can follow.

What additional requirements would these regulations create for your business?
GMPs_____ Site licences__16___ Both___7__ None__1___

1. GMPs will, of course, have greatest impact in terms of organization and costs. But a large plurality of members believe these costs to be the price to pay to be recognized as a world class quality supplier (whatever activity). Site licenses are basically an offshoot of the reformed GMPs and a control mechanism. They should be looked at as a management tool by our members. Both: For the medium term (3-5 years) the added costs of both measures will not be recoverable i.e. prices cannot be adjusted to maintain existing gross margins. On the other hand, cost of entry for new fledging competitors just became very steep.

3. Administrative duties.

10. None: No additional requirements since we currently hold a site license, only administration costs. We already follow GMPs and are inspected for meeting these.

21. Additional costs not already included in our cost structure.

23. From our understanding, only site licenses would be required. We are already in compliance with Canadian and foreign regulations

26. Both: Major difficulties to comply with the GMP guidelines C.02.004 see Point 11 interpretation (separate facilities for penicillin products, minor to moderate additional paper work)

Will these additional requirements have a significant impact on your business?
Yes__16___ No___8__

1. As seen above, these requirements will have a significant impact on most members' business.

3. As an importer, since there are no harmonized GMP's with our major trading partners, i.e., the US, and Europe, forcing Canadian GMP'S on our suppliers world wide will ultimately increase costs out of reach. We in this industry supply niche products to a niche group of people, all low risk, and this process (added to the already injurious effects of Part 1 and Part 2 Cost Recovery) will in effect stop most of these products from being available to the Canadian consumer through a legal Canadian outlet. They will continue to get these products by mail order or driving over the border, or from the underground economy, thus depriving us of legitimate sales, and of course the jobs that go with them.

6. The proposed implementation date of January 1, 1997 does not provide sufficient implementation time. License applications would be time consuming for Regulatory Affairs departments.

10. If a foreign site is licensed by Canada and a Canadian company imports product from them, there should be no additional charges related to importation.

11. No: However my Company uses wholesalers. The Rx side of our business wonders if the inclusion of wholesalers will have a serious impact on wholesalers or if wholesalers can absorb both the fees and GMP requirements without difficulty.

12. Yes: Primarily financial.

14. Yes: 1. Impact on management time and extra documentation control costs.
2. Increased complexity of overall business process.

15. Yes: 1. Foreign factories will be required to generate Site Master Files according to unique Canadian information requirements. (lacks harmonization)

2. Additional administrative burden for filing for ELS.
3. Additional cost of doing business in Canada

16. Unknown at this time

17. Yes: This will depend a lot on the amount of information that we are required to maintain in Canada versus our ability to rely on foreign inspection reports. If we are required to duplicate the validations and controls that our parent maintains, it is doubtful that we will ever comply with the licensing requirements.

18. The impact is dependent on how this process is administered. There is a potential for delays in product introductions and implementation of changes.

19. Yes: It is unclear at this point according to the discussion document, but written procedures, building inspections, conditions of storage, and lot/batch tracking (amongst the other items mentioned) will certainly add to our workload at a corporate and site level. Perhaps, we will add a person (s) dedicated to procedure documentation, ensuring conformity, and site liaising for site inspections.
Also, we will undoubtedly require information system changes (which are already under discussion) to handle lot/batch tracking ability

21. Yes: As custom manufacturer, we believe that some of our customers in regard to those new regulations will drop their Pharmaceutical line and resulting in a net loss to us of between 15 and 20% of our gross sales.

23. Yes: If internal audit reports are not acceptable, the additional requirements, whatever they turn out to be, will have some impact on our business as we have several foreign sites which manufacture drug products (time and cost).

24. No: Except for the license fees, we are already respecting GMP and GLP regulations. Our operating costs were already considerably higher than those testing facilities that do not respect GMP and GLP regulations!

25. Yes: A more bureaucratic system is being set up to issue annual licences. As far as GMPs are concerned there does not appear to be any change. New system will have more paper work for both the HPB and the drug manufacturers.

26. Yes: If GMP guidelines are applied ad literam to the veterinary drugs. Of major concern is Point 11 of the interpretation of C.02.004 that requires separate facilities for production of penicillin. Unless this requirement is waived for veterinary drugs, this could create major problems reducing to a fraction the number of manufactured products.

What activities within your business would be most affected by these proposed GMP and establishment licensing regulations?

	Positive	Negative	Prohibitive	No Impact
General Administration		12	1	11
Budgeting/Control		17	1	6
Financing/Investment/Taxation	1	10	2	8
Human Resources Management		9	1	11
Delivery/Distribution/Sales	2	5	1	14
Development of Products/Services	1	7	1	12
Supply Management	1	7	1	12
Marketing	2	6	1	14
Production		7	1	14
Customer/Client Services	2	2	2	15
Other		3	1	6

Comments:

1. *GMP requirements will have much greater impact than licensing fees and regulations. We are looking here at medium term impacts. One of the greatest impact will be on HR management and finding or training people with appropriate skills to efficiently carry out GMP requirements.*

3. *Prohibitive: Comments: See the cost calculation*

4. *The proposed fees will be factored into the annual budget and are paid out of cash flow thus having a minor negative effect on budgeting. Until the value of the establishment license is demonstrated to be greater than the value of the present GMP compliance inspection process, the fee will be seen as a subtle form of taxation. The effect on financing is short term and a consequence of repatriating manufacturing activities from contract manufacturers who are unable to survive the costs of licensing implementation and compliance with the new GMP guidelines.. The assessment of a negative impact on supply management is based on the assumption that smaller suppliers will be driven from the market by the costs of establishment licensing and compliance with the new GMP regulations and guidelines. The forced consolidation of small specialty suppliers will reduce competition in this area and conceivably result in higher costs. This affect is compounded at the contract manufacturer level by the costs they will incur in complying*

with the new GMP guideline particularly the area of validation. The positive effects are predominantly felt in the areas of sales and marketing. Their value is based on the assumption that a license issued by Health Canada will confer a competitive advantage in international circles. Historically, jurisdictions are extremely hesitant to recognize the value of such a license. As an example, Canada does not accept the GMP certificates issued by European countries as evidence of compliance with GMPs without a though review of written inspection data. Conversely, the United States will not accept other jurisdiction's assurances and will conduct independent inspections. The Drugs Directorate's efforts to negotiate MRA and MOU agreements are recognized, however, until this lengthy process is accomplished with major trading partners, the value of a license internationally is extremely limited

5. Selling prices will have to be increased. Limited specie products will not be launched

6. Supply management may have a negative impact if the company is waiting for a new dosage form class to be added to the company license.

7. Additional burden will be added to the administrative efforts which will take this time away from higher valued activities.
Budgeting, Financing and Investment will be impacted by the increased cost to produce a product which will impact our cost structure negatively.

8. If an establishment has its EL revoked and they are used by us as a third party manufacturer in Canada then this may cause supply problems.

10. We already adhere to GMPs.

11. No: {Note that I will refer to this comment in future as question #5} The revised C.02.019 wording would now seem to allow direct shipment from a US distribution centre directly to Canadian customers and remove the former requirement of having to receive a batch onto the importer's premises for at least identity testing prior to release and distribution. If this interpretation is correct, it is important for the distribution of drugs and in particular, drugs similar to cosmetics. It would harmonize the difference in the regs. between drugs and cosmetics with respect to distribution requirements. Drugs similar to cosmetics and cosmetics can often be found within a product line or even a given brand name as various versions of a brand. Allowance of direct shipment would significantly reduce the number of inventory days in the distribution process and eliminate or reduce the regulatory need for an importer's local distribution centre. This will substantially improve customer service and make supply management more efficient. Some downsizing of local distribution facilities may result in an impact on Human Resources management. Regulatory preparation of licensing submissions, site reference files, etc., will increase workload.

14. 1. Additional costs(including fees, preparation and maintenance of Site Reference Files and other associated administrative processes) must be reflected in budgets.
2. Additional human resources required to prepare/maintain Site Reference Files for domestic

and foreign facilities. 3. Requirement to prepare and maintain a Site Reference File for all manufacturing/packaging sites will lengthen the overall process of product development and therefore extend the time to market(ie) increased development cycle time. 4. Additional interaction will be required with suppliers to coordinate the preparation and maintenance of Site Reference Files.

15. Additional cost of business in Canada, administrative burden for filing licence, preparation of SMFs takes away from activities that add to research and development of medicines for Canadians.

18. potential for negative impact dependent upon eventual means of administration implemented by HPB, ie, it appears that there will be a 2-tiered process for review and approval of license requirements including the Drug Submission review personnel and Regional Office personnel. Will have to implement additional internal processes to maintain establishment license and appropriate payment of fees.

19. It is unclear which areas will be most affected, but certainly our corporate logistics and I/S staff will be impacted due to system and procedural changes and documentation. Whether the change is positive or negative is unclear.

20. Quality Assurance and Regulatory would be greatly affected in terms of cost and time.

21. As described earlier with a net loss of sales, all departments will be negatively affected putting the company in a situation of rationalization costing jobs and affecting future growth.

22. Developing and obtaining documentation for suppliers from other countries. Increased costs for no perceived value.

23. Again, the uncertainty surrounding the possible ways to certify foreign sites makes it difficult to understand whether there will be a major impact in the compliance area of the company.

24. Our company has already adopted GMP practices. There is nothing in the 4th ed. Of the GMP's which will have an adverse effect on our company. Except for the additional licensing fee, these proposed GMP's have no effect on us.

26. We cannot begin to see any advantage from our point of view, particularly in as much as the intent is to include veterinary establishments within the same framework as for human sites. Separate GMPs are an absolute must for the veterinary market.

POTENTIAL IMPACT ON YOUR BUSINESS

How would these proposed GMP and establishment licensing regulations affect drug products sold by your business?

Would the quality of your products be affected?
Positive_____ Negative____1_____ No Impact_____22____

3. Just the costs.

4. (This company) consistently strives to manufacture medicinal products to the high quality standards. The proposed licensing regulations would not result in any impact on individual product quality.

6. (This company) participates in the QUAD program and complies with current GMP therefore the quality of our products would not be affected.

10. No Impact: We already comply with GMP regulations.

16. Not applicable to a testing lab.

17. No impact: There would be no impact on Quality as we already meet these requirements at the site of manufacturing

24. The question is not applicable. We do not sell products.

25. No impact: requirements to be in GMP compliance will not change.

Would it affect recognition/acceptance of your drugs products?
Positive___3_____ Negative____1_____ No Impact_____19____

3. Increased cost, decreased consumer acceptance, decreased sales.

5. No Impact: Probably not since our customer's don't ask about our GMP status.

9. Uncertain at this time

10. No impact: No, our products and Facilities are already (and always have been) expected to comply with GMPs globally.

12. Negative: Licensing fees would eventually affect product price. Increased cost could cause some existing or potential customers to decide against the purchasing of our products (nutritional supplements).

15. No impact: We currently manufacture products meeting GMP requirements

17. No impact: The customer will not know any change has occurred. The proposed possible benefit of Canadian certification that we meet GMP requirements for the provincial formularies is not real as current inspection reports are accepted as proof of GMP certification.

18. Dependent upon HPB's successful implementation of MRA's with Japan, EC and USA

19. Positive: Regulations would probably heighten our standing in the market, although if there are not compliance penalties it would remain unclear as to who was complying.

21. Positive: No impact on Domestic
Positive if foreign regulatory agency accept Canadian GMP inspection reports.
This will eliminate certificates of free sale and certificates of Manufacturing compliance.

Would it affect access to existing or potential markets?

In Canada:	Positive____3____	Negative____7___	No Impact____15____
In other countries:	Positive____6____	Negative___4____	No Impact____16____

1. (Positive in Canada) It is likely to have a negative impact on custom manufacturers. Most distributors of marginally profitable products are likely to abandon these products because of the added costs. These were in most instances a considerable contribution to custom manufacturers' volumes.

2. The perception that if licensed we meet regulations might have greater positive impact than the current situation

4. The access to markets could benefit if the international community is ready to accept the premise that a license is evidence of GMP compliance. Until the necessary MOU and MRA are negotiated and approved, the international utility of a license is limited. Additionally, there is a disturbing possibility that global acceptance could be hampered for regional political reasons regardless of their confidence in the similarity of GMP requirements.

5. No Impact: Customers know that currently in order to sell in Canada, we need to GMP approved. The additional licencing requirement won't change that.

6. Positive & negative: Access to potential markets may be positively affected by having memorandums of understanding with other countries however, there may be a negative impact caused by delays in license issuing process

10. Positive impact if it will facilitate and implement mutual recognition agreements with other developed countries, i.e. acceptance of inspections to foreign governments. Schedule D drugs were specifically excluded from GMP regulations, we can now definitely state and have government declarations stating we meet GMP. This is important for foreign licensing activities.

11. No: (See question #5). Positive: A more cost effective distribution network would favour greater market penetration. Our Canadian company does not export drugs so the other country part of this question is not applicable.

12. Negative: Importation of foreign manufactured products would now require a foreign GMP inspection fee and possibly the need for a MRA or HBP inspection. This expense could exclude products from consideration. Additional fees would increase the price of Canadian products in foreign markets. This is an added expense that the foreign manufactured products would likely not have. Therefore, Canadian products would have a relatively higher price and a market disadvantage.

14. Negative in Canada: Potential for negative impact where country of a foreign supplier being considered is not subject of an MOU or in future an MRA.

15. Positive in other countries: If MRAs for GMP inspection reports are implemented then we will 'be able' to compete for the right to manufacture for these markets more easily. For example, if the FDA recognizes Canadian GMP and pre-approval inspection is not necessary then the approval process should be simplified and faster.

17. Negative impact in Canada would be related to our ability to duplicate the necessary documents from our parent company.

18. Negative: To date, Canada has benefited from flexibility inherent in current regulations and guidelines. We currently have the ability to respond to export markets in a timely manner . The proposed changes may eliminate this ability in Canada.

21. Negative: Dependent on the ability to establish reciprocal agreements with major trading countries.

Would it affect timing to market?
Positive___1_____ Negative____9_____ No Impact_____13_____

5. Negative :Each new product type requires an amendment to the licence so it depends on what new products we want.

6. Negative: Companies in a start-up or growth phase may be negatively affected. When a decision is made to add a new dosage form onto the license, there would be a delay from the time that the company is ready to manufacture until the license is approved. This would be more critical for contract manufacturing companies. Potential manufacturing sites (particularly non Canadian) may not have obtained EL or have outstanding issues which need to be resolved.

11. Positive: (See question #5)

12. Negative: The need for foreign inspection / data would delay time of new product

introduction.

14. Negative: Site Reference File preparation for foreign sites, time to develop/educate the site regarding requirements and to prepare and maintain the new documentation requirements will add extra time to the process for market introduction.

17. Negative: The time that it takes to certify a new dosage form may negatively impact our ability to get new products to market. This is dependant on the delay from the time of application to the approval of certification.

18. Negative: Negative impact is possible if regional office and inspector do not fully understand new product/process or arbitrarily impose requirements on license approval/continuance/renewal. Also dependent on level of bureaucracy involved for administration of program at both the regional and national levels. Importation has potential for being negatively impacted if HPB decides that a foreign facility inspection is warranted.

20. Negative: Waiting for preapproval inspections.

25. Negative: A new product or a new dosage form can be produced and introduced to the market only after the facility has been licenced for that purpose. One can anticipate

Would it affect flexibility to meet customer requirements?
Positive____2____ Negative____7_____ No Impact_____16_____

1. (Negative) Especially should these requirements involve changes in GMP related procedures.

3. Our customers want specialized, niche products. The natural product shopper reads health books and magazines, and has decided for themselves to take control of their and their families health care, through improved diet, and specialized supplements, herbs, and homeopathic remedies. These products are generally regulated in the United States as "food supplements", and generally in Canada as "pharmaceutical drugs". The products we import tend to be specialty, and in very small runs. Many of our suppliers are themselves marketing companies, and purchase their requirements from different manufacturing plants. All this means is that the costs of plant licencing will be prohibitive, and we will be forced to stop selling many of these products, and the jobs we create will move to the United States or offshore.

11. Positive: (See question #5)

12. Negative: As above, also would affect switch of current product to new suppliers for same reason. This type of delay could cause out of stock situations and customer dissatisfaction.

18. Additional level of approval for license can negate flexibility due to license application process. It appears that HPB is regulating the approval of changes within a company.

This added level of approval appears to add to the overall bureaucracy of the program and may discourage companies from making changes to meet customer requirements.

25. Negative: If a customer needs a new dosage form and the facility is not licensed for the dosage form, there will be delays.

26. Negative: If proposed GMP guidelines will apply "as is" to veterinary products, the need for separate penicillin manufacturing sites will severely reduce the product range.

Would these proposed GMP and establishment licensing regulations affect general business conditions for your business?

Would it affect relationships with other businesses (subsidiaries, agents, joint ventures, partnerships, distributors)?

Positive____3____ Negative_____11____ No Impact_____10_____

1. Stabilizing effect on market (less switching of custom manufacturer for ¼ cent difference in price) Negative impact on importers of small volume products from many foreign suppliers.

2. Positive: The concept of being licensed may yield a more positive image.

3. Negative: For the same reasons as above

4. The existence of a license would not remove our corporate responsibility to qualify and audit firms we choose to source products and expertise from. In the longer term, the licensing proposal has the potential to skew the market towards larger firms who are more capable to finance and administer a mandatory license program.

Potentially, a minor advantage may be conferred on firms with valid licenses who compete internationally to custom manufacture if the necessary agreements (MRA,MOU) are negotiated.

8.- Could be negative. What if a major manufacturer is not granted license due to part of their operation that does not affect our product, i.e. parenteral operations vs. ethical.
Would need assurance from 3rd party manufacturers in Canada that EL have been issued and in good order.

9. Negative: Potential exists to disrupt existing contract manufacture arrangements.

10. No, in our business, facilities and products must be licensed.

11. Positive: If the interpretation of C.02.018 and C.02.019 permits direct shipment from US distribution centre to Canadian customers one result will be a closer relationship between suppliers and the importer via Q.A. organizations.

12. Negative: Our products would incur cost increases not required in other countries. Corporately, this could lead to products being manufactured in countries other than Canada, for the global market. Higher prices could result in lower sales of imported / distributed products, affecting the income and profitability of our business partners.

14. Negative: 1.The new requirements indicated above will impose additional conditions on current and potential suppliers.
2. There will be new business costs and different contractual relationships to execute.

15. No impact: Positive - Mutual Recognition of GMP Inspections when implemented will allow for greater ability to compete for the right to manufacture on behalf of (this company) for world markets. Negative - The ability to import from foreign factories will be limited to those with a MOU or MRA (future). Adding new factories for new products, the additional establishment licence cost will increase cost of doing business.

16. Positive: By being licensed and monitored it would be possible to offer a certified service to our clients which would be a good marketing tool.

17. Negative: Our parent will generally see Canada as a difficult area to meet regulatory compliance and therefore be less likely to invest in Canada.

18. Licensing process could require amended contractual agreements to encompass responsibility and liability for maintenance of licenses at various partner locations. Recovery fees would have to be considered when negotiating out-sourcing contracts.

24. No impact: We are already applying GMP in our work.

25. Negative: More paper work, inspections , reviews of reports issued by other jurisdictions.

26. Negative: See above.

Would it affect relationships with other organizations (academic or research)?
Positive___1_____ Negative____3_____ No Impact_____21_____

4. There would be an effect if the licensing proposal is extended to CROs in addition to analytical testing laboratories. We cannot afford to accept the license of a testing or analytical laboratory as representative of their ability to satisfy our demands.

5. Negative may choose to use a contract lab for drug testing to avoid licencing our own facility.

6. Negative: It may have an impact on working with academic organizations if they are not licensed for certain activities. An example may be for doing contract manufacturing for clinical supplies

12. Negative: Increased costs associated with licensing fees will make fewer finances available for

research.

Would it affect other external factors (legal, liability)?
Positive___3_____ Negative_____3____ No Impact_____18_____

1. Greater emphasis on foreign suppliers' compliance to GMPs.

4. Positive: By licensing all levels in the production chain, the HPB would be accepting liability for the performance of licensed firms and greater liability for the final product performance. Thereby, lessening the DIN holder from being held solely liable. It is conceivable that the dilution of liability will translate into lower insurance costs for individual manufacturers previously held wholly liable for product performance.

8.- Could be negative if a 3rd party manufacturing has their EL revoked and thereby results in supply problems or recall situations. Contractual arrangements would be needed to make sure they meet EL req.

14. Negative: New contractual agreements with suppliers and legal frameworks to execute may add ramifications not clear at this time.

15. No impact: Legal liability will be shifted from industry to regulatory agencies. The regulatory agency will now have to partner with industry to ensure foreign factories meet GMP

18. Responsibility for maintenance of an approved license will need to be established such that liability in terms of non-compliance with the amended regulations does not become an issue. (eg. with Wholesalers, Testing Labs, Distribution Organizations, etc.) In the event of delays in approval of a license amendment, our commitments to supply domestic or international markets may be affected and contingencies will need to be built into the process.

What operational changes in your company would this regulation require?

Would it affect personnel? (Hire, Redeploy, Dismiss, No Change?)
Hire___6___ Redeploy___10____ Dismiss____5____ No Impact_____9____

1. As stated above this will be major challenge

3. We would have to have more people work in Q.C., but as we anticipate a severe decline in Sales because products are no longer available to us, we will have to cut staff....These jobs will be exported to the United States and elsewhere.

4. There would likely be a modest increase in the number of employees responsible for maintaining the dialogue with the HPB and compiling documents to satisfy the site reference file requirement. The added regulatory burden of compiling and maintaining the site reference file cannot be measured accurately but is likely to be significant. The

data requirements for the site master file have not been adequately discussed and, while the assertion that the site reference file will be brief is recognized, past practice within a bureaucracy has demonstrated that the additional regulatory requirements never lessen a paper burden. Estimates of the work required to compile and maintain the proposed site reference file cannot be undertaken without concrete guidance. This added workload would be undertaken in addition to other regulatory duties and preparation of submissions for approval.

6. Redeploy: Some Quality Assurances resources may be redeployed to Regulatory Affairs. In order to apply and keep application information current there would be additional administrative work required.

7. Depending on the magnitude of the fees in the future, in order to maintain a competitive cost structure versus other company plants around the world, it could result in a downsizing of the workforce in order to generate a competitive cost structure to allow us to receive worldwide manufacturing mandates.

8. Potential for reduction in QC staff if GMP changes from MRA e.g. reduced requirements for testing in Canada. Resources for SRFs.

10. Minimal: May require additional administration assistance.

11. Redeploy/dismiss: As per question #5, some redeployment of Canadian distribution centre personnel may occur. In addition, the type of staff in Canadian Quality Control may be altered to lessen laboratory Q.C. content while increasing Quality Assurance content for managing foreign fabricators/packagers in ensuring compliance.

12. Redeploy: Personnel may have to redeployed to administer / conduct foreign licensing and GMP inspection programs. Longer term, the potential increase in expenses may eliminate our ability to hire additional staff.

14. Hire: 1. Extra documentation/control activity personnel driven.

2. Foreign supplier education and associated documentation/control issues are personnel driven.

16. Hire: This would probably entail a need to higher more QC/QA personnel.

17. Redeploy: As this is a regulatory requirement and not a business opportunity we would not hire to meet the need, however we would require a redeployment of personnel to ensure we meet the requirements. This would likely mean readjustment of standard times expected for internal reports.

18. Hire: The overall impact in personnel is unknown. To provide a thorough analysis, specific detailed requirements resulting from the changes would need to be known.

19. Hire: Depending on the nature and extent of operational requirements and procedural

changes we may be required to hire additional staff to conform to the new regulations, or temporary employees to assist during the transition period.

25. Redeploy/dismiss: It is conceivable that one of the two distribution centre will close affecting personnel.

26. No impact: Unless the decision is taken to shut down our facilities.

Would it affect current operating procedures?
Minor___11__ Major__4___ Prohibitive___3___ No Impact____6_____

1. Will have to re-examine

3. Prohibitive: The cost of administrating

4. No Impact: As a GMP compliant manufacturer, (this company) has a procedure for the writing and revision of SOP for all critical activities within the manufacturing environment. SOPs to address the additional procedures will be handled using the existing process.

5. Minor: Shuffling responsibilities to handle additional work load of Site Reference File and to ensure changes to regulations are understood and followed.

10. No Impact: Already comply with licensing and GMP.

11. Major: Quality Assurance will be more focussed on validation/contractual agreements, with foreign fabricators/packagers, and systems to ensure that only Canadian acceptable product crosses the border and that controls over distribution are adequate to Canadian needs. Our focus will be shifted to proactive Q.A. activities prior to shipment to Canada, and less toward the reactive repeat testing currently required post shipment.

12. Minor: Increased administrative costs due to licensing fees will increase the relative cost of manufacturing services, decreasing the amount of work conducted. Rate of growth will be slower, affecting plant capacity and utilization projections.

14. Major: Establishment licensing will add extra process detail to ongoing compliance activities associated with Drug Submissions and GMPs.

18. Change control process would be affected if it must include license amendments and in some cases approval from HPB prior to implementation.
Site Master File preparation and maintenance will be a new process.
There will need to be an increased focus on Supplier/Contractor GMP audits/ Contractual Agreements.
Responsibility for maintenance of license and payment of fees must be established internally. Budgeting procedures will be affected.

19. Major: We have stated that there will be major operating procedure changes as the change to lot/batch tracking is significant on its own. However, other operational changes are unclear.

21. Prohibitive: The general effect would be to create a situation where we need to consider the additional costs and dwindling sales due to the implementation of these policies. It would be more to the point and easier to manage if this was a % of gross sales.

23. Minor: If the current method of establishing compliance for foreign sites is not acceptable, our internal operating procedures will have to change.
Procedures will also be set up to prepare the Site Reference File (no guidelines yet, so it is difficult to assess the overall impact).

25. Major: The requirement for annual licenses for various facilities/ for new dosages/ for new categories of drugs will change our current operating procedures.

26. Prohibitive: See next entry

Would it affect facilities or equipment?
Add__1____ Modify___6__Close Down___3___ No Impact_____14_____

4. Add: The very real likelihood that the licensing scheme will force smaller contract players out will require that we repatriate manufacturing capacity. In addition, current equipment will be upgraded to comply with manufacturing needs.

8. Could cause closure of small companies. Potential for modification of facilities to meet Canadian requirements.

9. Modify: Only to the point that required changes have been identified and earlier than planned expenditure will be involved

11. Modify: Reduction in the Canadian distribution centre. May affect size of Canadian chemical and microbial quality control testing laboratory.

14. No Impact: See response to following question.

18. The effect on this is unknown and is dependent upon specific detailed requirements of the program.

19. 19. Modify: There is probably no impact but we may be required to change storage methods, and certainly will alter information systems to support lot tracking.

25. Modify/Close-down: There is a possibility of reducing from two distribution centres to one.

26. Close down: Unless separate veterinary guidelines are annexed to the GMP guidelines, we

will have to consider a close down with a loss of up to 50 permanent jobs.

Would it affect utilization of productive capacity (+/-%):
Positive___0_____ Negative____3_____ No Impact_____18_____

4. No Impact: There would be a slight increase in the utilization of overhead due to an increase in production volume. There would be no impact on the utilization of current production capacity, additional capacity will be installed.

14. No impact: 1. Although there is no clear rationale for Establishment Licensing as a concept to impact an operation on the fronts proposed by this and the preceding question, there is always the potential for any regulatory initiative to drive the process of rationalization. 2. The need to continually evaluate capacity utilization is ever present and on the positive side out sourced activities could be rationalized to internal activities where a cost advantage is demonstrated under the new circumstances. As well, the opposite could be true where rationalization yields a close down decision

17. This is hard to access however our company is already functioning a virtually full capacity and as we would not increase staff, it would result in lower priority jobs not being completed.

18. There may be a positive or negative impact on this dependent on the level of bureaucracy developed at HPB for license approval/suspension/renewal. If there is an increase of bureaucracy, the effect will be negative in that response to export markets will be affected. If there is a decrease in bureaucracy, the effect would be positive or neutral.

21. Negative: -20%

25. Negative: Two distribution centres are considered more efficient than one for our business. If they are combined into one, the overall productivity will be negatively affected.

26. Negative: Assuming special consideration for veterinary guidelines are not taken, more than 70% of production capacity will be lost.

Would these proposed GMP and establishment licensing regulations affect product development strategy and/or introduction new/improved products or services?

Would it affect product development?
Positive____1____ Negative_____10____ No Impact_____14_____

3. Negative: We would have far less, far fewer, innovative new products available to us

4. No Impact: The affect on product development would be in planning to source activities and materials including analytical services, from licensed (not necessarily synonymous with qualified) suppliers. With respect to their qualifications, (this company) rigorously

qualifies our potential partners.

5. Negative: We'd have to be careful what types of products we choose to develop and who we have manufacture them to avoid changes to our licence.

6. The fees are not restrictive for a larger company therefore, they would not be considered in expanding to different dosage form classes.

8. Hold ups could arise getting the EL.

12. Negative: Additional costs associated with investigating new drug categories / suppliers could be prohibitive.

14. Negative: 1. Generally speaking it is judged that there would be little or no impact on this aspect of development. 2. The added requirements of Site Reference Files may affect decisions regarding choice of suppliers based solely on the ease of qualification under the new circumstances of licensing of any given supplier.

17. Negative: If we required a new license for a new dosage category product development would be negatively impacted.

18. Negative: Timing of new product introductions may be affected if any delays in amending establishment licences are experienced.

20. Minor negative impact to Canadian subsidiary.
No impact - International

26. Negative: There is less likelihood that we would continue to develop products to be manufactured in our local facility if proposed GMP guidelines are implemented for veterinary drugs "as is".

Would it affect overall R&D?
Positive____0____ Negative____8_____ No Impact_____17_____

1. Competing for non elastic resources : money

3. Negative: We won't have the funds, through less profits. Also because we have short runs, etc., it won't be worth it.

5. Negative: It may make sourcing from foreign countries prohibitive

12. Negative: Increased costs associated with licensing fees would make fewer finances available for R&D.

14. Negative: Overall impact on the increased development cycle time.

18. Negative: The current regulatory climate in Canada has been favourable to and supports development activities. Changes proposed may affect a firm's ability to attract investments in manufacturing developments in the future.

23. Negative: There would be some affect on the compliance side (ie. to verify foreign site compliance and to establish the Site Reference File). Since I don't have the guidelines for the Site Reference File, it is difficult to tell how much work will be involved.

26. Negative: See above.

Would this proposal affect your business investment or growth strategy

Intention to invest/expand (acquisition, franchise, in-house expansion)
Positive___2_____ Negative_____10____ No Impact_____12_____

1. Negative: for 3-5 years

3. Negative: Higher costs, and less products to sell, means less investment, less jobs

4. No Impact: The costs per site in additional licenses would be factored into the decision to expand by purchasing existing facilities and weighed against constructing new facilities on our present property.

5. Negative: Acquisitions will be narrowed to avoid licensing another site.

9. Negative: In the continuing absence of any political will to halt the illegal activity referred to earlier, further investment in this market has to be re-evaluated.

11. Positive: Assuming direct ship interpretation is valid, significant cost reduction will permit either reduced cost to consumer or greater expenditure in Canadian advertising investment. Either approach will grow the business.

12. Negative: On a global scale, our corporation will continue to develop a negative feeling about production from a Canadian facility if our administrative costs continue to increase. The likelihood of a plant closure continues to increase. This has already occurred in our associated facility in (city).

17. Negative: As stated above, our parent company would view Canada as a regulation prone country and therefore less attractive for investment than other markets.

18. Negative: The regulatory climate in Canada has been viewed positively by investors. Changes to this climate may cause Canada to lose this advantage. May affect specific construction plans of new facilities since fees are partly based on number of buildings.

21. Negative: Negatively affect our ability to compete within out company worldwide as a

manufacturer.

The additional requirements and associated costs along with other aspects of cost recovery may lead to a decision by our parent company to reduce its investment in Canada and source products for Canada from other countries.

26. Negative: Obviously, if we are further regulated w/o Health Canada having addressed our concerns/needs.

Intention or ability to divest (closure, sales of assets)
Positive___2_____ Negative_____5____ No Impact_____18____

3. Negative: See note above

11. Positive: Canadian distribution of drugs via Canadian distribution centres may be impacted resulting in some capacity reduction.

18. Negative: May affect the company's ability to divest in other markets if it becomes more difficult to manufacture in Canada due to extra regulatory hurdles and lack of knowledge on whether the proposal will result in any delays in granting of licenses to manufacturers to supply foreign markets.

Ability to restructure (mergers)
Positive____2____ Negative_____8____ No Impact_____15_____

3. Negative: See note above

6. Negative: As written there would be a disincentive to acquire different sites.

12. Negative: As stated above, there is a growing corporate wariness about increasing investment in Canada. The purchase / merger of a second facility would now double our licensing fees.

17. Negative: New site licenses would presumably have to be generated making the regulatory impact of a merger more of a burden.

18. Negative: On a corporate-wide level, the proposal may affect our ability to restructure manufacturing facilities on a global basis since extra regulatory requirements now introduced for manufacturing different product forms in a single facility.

Would it affect continuous improvement/quality management methods?
Positive____5____ Negative____3_____ No Impact_____17_____

3. Negative: See note above

11. Positive: Allowance of direct ship furthers North American harmonization. So also will likely be the outcome of Mutual Recognition Agreements. Both are good for GMP and

Quality Management because harmonization minimizes the need for different standards and duplicate systems reducing risk of confusion and error and allowing greater focus on development of robust streamlined systems.

12. Negative: Increased administrative costs due to licensing fees will make fewer finances available for programs such as these.

18. No Impact: We would have to build the new requirement into our new product introduction plan to ensure no delays are experienced if we have to wait for licenses to be granted.

19. Positive: It would probably enable us to improve quality and standardize methods, but this is unclear without site inspection and operating guidelines.

21. Negative: We already must comply with GMP regulations.

Would it affect your intention or ability to adopt new technology?
Positive_____1___ Negative____8_____ No Impact_____15_____

1. For a period of time, validation of processes will freeze technology introduction in manufacturing.

3. Negative: See note above

11. Positive: North American harmonization creates greater economies of scale which positively impacts development of new technologies.

12. Negative: Increased administrative costs due to licensing fees would make fewer finances available for the procurement or improvement of technology.

14. No impact: On the positive side, where a significant technology in documentation control existed and had not been adopted, the new circumstances could speed up approval for implementation.

17. No impact perceived at this time.

18. Requirement for HPB approval of "changes" could have a dramatic negative impact based on historical experience with HPB's lack of commitment to "come up to speed" quickly on new technologies (ie resource issues, resistance to being the first Regulatory body to approve new technology/ideas, uncertainty in application of new technology to existing standards)

19. Negative: We would be restricted to new technologies that support individual lot and item tracking.

Would it affect your strategic planning?
Positive___3_____ Negative____7_____ No Impact_____14_____

3. Negative: See note above

12. Negative: Planning programs would have to adapted based on anticipated impact of licensing fees on a case by case basis.

14. No impact: Cost Recovery as an implemented strategy of the Drugs Programme in Canada adds another external factor to be considered by a pharmaceutical business in its strategic planning analysis of the environment in which it operates and how business costs can be managed versus profit maximization.

15. Negative: It could reduce sourcing needing new medicines especially for limited use by only a small segment of Canadian population from new factories as the cost of filing the submission and obtaining an establishment licence could be prohibitive relative to potential earnings. Also if the source of the medicine is in a non MOU/MRA country then we could not access it.

18. May impact in a positive way if foreign markets recognize the establishment licenses as indicative of high quality and it becomes easier to export to them. May impact in a negative way if any delays are experienced, or regulatory requirements make it such that manufacturing in Canada (and associated flexibility) is no longer attractive to other markets in terms of meeting their customer requirements (i.e., license amendments).

21. Negative: For sure with a decrease of our sales, we will definitely be less interested of investment in Canada and we will look for new opportunities outside Canada

26. Negative: For reasons previously mentioned

COST RECOVERY

Did the Fee Calculation Form help you understand and calculate the appropriate fees for your business? Yes___19_____ No___6_____

1. Yes: except for an accurate evaluation of costs linked to foreign suppliers.

2. Yes: However, instructions do not indicate that Fabricators who also import, do not have to include the analysis and controlled substances component in Block 2 calculations.

6. No : There was confusion on how to calculate the cost of having a warehouse for distribution at another site

8. The discussion document did more to explain the correct method of calculating fees than the fee forms. Some of the items seemed to differ between the fee form and the discussion paper.

10. No: It is not clear how to interpret "# Drug Categories" or "Total Dosage Increment Fee". This would be almost impossible to understand if English were a second language. The existing form needs to be edited to clarify definitions of "building". A guidance document is required particularly for the "GMP inspection component" in blocks 1 &2. Tables should be provided indicating drug category and dosage class (as in Table 1 August Consultation document Appendix E)

11. No: My packaging operation in (city) (it labels the filled imported packages with Canadian labels) is also the importer/distributor for our ethical drugs. I believe the forms have caused me to double count. For example the lab looks after both the filled unlabelled imports and the final labelled packages. It would have been more accurate to complete the Importer section and just make a small base charge for inspection of the local packaging operation.

14. Yes: Business complexity is not clearly exposed in the examples given. For example, dosage form class "solution" needs clearer definition(ie) homogeneous as well as heterogeneous or is the latter considered to be a suspension.

15. Yes: The information on how to calculate fees was put on the HPB bulletin board on September 3, 1996. The form itself was not sufficiently clear, i.e. analysis fee, do we pay for each type (controlled substance and pharmaceutical), how do we pay for importation activity using fabrication.

17. Yes: Although I could not get the Excel spreadsheet to calculate.

20. No: Information & Definitions not clear.

21. Yes: But subject to interpretation.

Based on the fees you have calculated, do you feel that the number of sites/buildings that you operate would be affected?
Increase___0____(#) Decrease_____4____(#) No Impact_____20_____

3. Decrease: We would lose suppliers (akin to sites) that would not want to carry the extra cost of licensing

12. Decrease: One foreign supplier and their distributed product would likely be discontinued.

15. No impact: The regulatory burden of changing sites to reduce the number of buildings/sites is far greater than paying the establishment licence.

24. No impact: Our testing laboratory consists of only one building.

Would the type of products or dosage forms offered for sale by your business be affected?
Yes____6____ No____17_____

*1. No: * More likely yes in the case of custom manufacturers*

2. Yes: Low volume service products that require specialized processes and therefore are purchased from foreign site, might be discontinued.

3. Yes: We would end up with far less products to sell for the reasons already mentioned.

4. The choice of dosage forms and products is driven by the likelihood of our success in the marketplace and not on the costs of licenser. The costs of licenser will become « just another cost of doing business » .

8.- Addition of new manufacturing sites would have be weighed for cost and administrative burden.

12. Yes: As mentioned above, our only liquid product is distributed for a foreign manufacturer. This would likely be discontinued due to the burden of carrying so many expenses.

Would product prices be affected (or services, in the case of testing laboratories)?
Increase___8_____ Decrease____2_____ No Change_____13_____

3. Increase: Estimated (25%) based on the increased cost of doing business.

6. Increase: The prices would be affected since this would increase the overhead and operating costs. The increase would be minimal since it would be spread over all product lines.

8. We would expect that our Canadian 3rd party manufacturers would have obtained their own EL would, as a result, pass this incurred cost onto us.

9: Potential increase is justified but market place may not permit it.

10. Possibly increase: Product prices would possibly increase due to the increase in cost and overheads to operations.

11. Decrease: If my interpretation that direct shipment from US distribution centre to Canadian customers is valid there will be a change in the value equation and price decrease in a possibility. I am not able to estimate %.

12. Increase: While it is too early to calculate the exact impact, product prices will have to be increased to reflect our increased administrative overhead due to licensing fees.

14. No impact: Would expect the affected groups to pass on the increased cost of doing business to their customers, although in today's economy one would expect some attempt at accommodation and examination for other areas of cost saving to offset the increase, in reality a form of tax.

16. Unsure at this time

17. No impact: Our costs will be affected which will eventually put added pressure on the bottom line and in an unregulated pricing environment result in price increases. The price of new products coming to market will have yet another reason to ensure they are maximized.

18. No impact: In the future may have an impact on decisions to out-source testing or build contingency plans for currently manufactured products.

22. Negative (0.5%) These costs included with phase 1 and phase 2 costs will result in the above percent increase.

26. Increase/decrease/no change: Difficult to determine in the case of suppliers.

Would sales revenue be affected?
Positive__2____(% of sales) Negative___6___(% of sales) No Impact____16_____

1. No Impact: Negative in the case of custom manufacturers

3. Negative: Approximately (20%). It's difficult to determine which suppliers would want to "pull-out" of the Canadian market.

4. Sales revenues would only be affected outside of Canada if the license is realized as a competitive advantage. The domestic effect is likely too small to measure.

8. If price increases are required as a result of ELF, this may in turn affect the price of the products at the consumer level. This price increase could affect consumer purchasing decisions and ability.

7. Depending on the final fee it could have a significant impact on the formulary status of our products, since the formulary will not permit us to increase our price and obtain reimbursement.

11. Positive: Significant cost reduction would grow the business perhaps through price reduction or increased advertising support that the cost reduction would fund. Hence, revenue should increase. I am not able to estimate %.

12. Negative: Minimal impact.

14. No impact: A matter of the ability to absorb versus product pricing increase to protect revenue base.

16. It is felt that these proposals would have a significantly positive effect on business but to the exact extent is still unknown.

17. No impact: No impact on Sales revenue, however dollars available for investment will be reduced.

21. Negative (-20%) As explained previously.

To what degree would payment of these fees affect your cash flow?
Minor___13____ Major____2____ Prohibitive__1____ No Impact_____9_____

1. Minor: Prohibitive in the case of contract manufacturers and small import operations.

3. Prohibitive: Our annual profits are not too far above the annual fees we calculated

4. Minor: The licensing fees are paid out of cash flow and not financed separately. The added cost of establishment licensing is incidental in comparison to the annual costs already incurred for review activity and DIN notification.

10. Minor: This is difficult to assess until total costs are determined.

15. No impact: Budgeting of fees for establishment licence diverts funds from development of new medicines.

18. Minor: Must ensure correct amounts are budgeted, including potential for license amendment fees and new foreign facilities as alternate sources of supply.

To what degree would payment of these fees affect the profitability of your business?
Minor___17____ Major___1_____ Prohibitive__1____ No Impact_____6____

1. Minor: Same as above. One must also consider the cumulative costs of these fees and GMP

implementation.

2. Minor: Any cost increase will reduce profit unless some other offsetting improvement is found.

3. Prohibitive: See note above.

4. Minor: The generic industry is considerably more price sensitive than the innovator industry and as a result, costs cannot be passed to consumers without influencing market position. Increased costs without price flexibility will translate into lower profitability.

10. Minor: Payment of these fees would increase overhead/operating costs.

18. Minor: Minimal impact. Slightly increased costs of doing business.

To what degree would these fees affect availability or cost of financing (where applicable, this includes your ability to compete for a share of the budget within a multinational corporation)
Minor___8____ Major____2____ Prohibitive___0___ No Impact____15_____

17. Major: Although the fees are not high, the fact that their are fees will be yet another reason not to locate investment in Canada.

To what degree would these fees affect your ability to weather major financial fluctuations (i.e. fluctuations in the business cycle)?
Minor___8____ Major___2_____ Prohibitive___1___ No Impact_____14____

1. Significant: Major in the case of custom manufacturers

3. Prohibitive: As per note above, less profits mean an increased vulnerability to fluctuations

8. Again, profit margins for consumer products can be very slight. Many OTC medications are considered to be luxury purchases and even very minor price increases can push these out of reach for portions of the general population.

To what degree would these fees effect your business' ability to maintain long term return on investment
Minor__12____ Major___1_____ Prohibitive___1___ No Impact____11_____

1. Minor Major in the short to medium terms, could be prohibitive for custom manufacturers.

3. Prohibitive: As per note above, less profits hurt all aspects.

What cumulative affect will fees levied by the federal government have on your business?
Minor___13____ Major____8____ Prohibitive___2___ No Impact_____1_____

1. Cumulative effect of fees in all three phases plus GMP requirements very significant and prohibitive for some members.

2. Added to previous cost recovery fees, the total is becoming significant. While indicating "major" may be too high, it is definitely more than "minor". There is a real concern if fees escalate or if there are continual additional fees.

3. Prohibitive: As I've said earlier, we are a niche provider, and the cumulative affects of DIN application fees, DIN license fees, and now these fees are crippling. When treasury board announced cost recovery for our industry, they stated that total fees should not exceed 1% of the total sales of the companies involved, or words to that affect. What a "joke"! Before Part III, we are already way over the 1% cost rule.

4. Major: The annual federal government fee burden for (this company) is projected to be $500K annually. This figure is comprised of the fees for DIN notification, review and establishment licensing. To absorb this additional cost (1-2%), profits from sales have to increase approximately 9%.

6. Minor: The cumulative fees levied by the government are becoming a consideration in budgeting and expansion however, the fees for licensing are the smallest component.

8.- All three phases of cost recovery fees once implemented will amount to approximately $145K per year (assuming one major submission per year). This amount is not easily absorbed nor transferable to consumers and patients. Phase three of these proposed cost recovery fees would amount to approximately 10% of these costs.

10. Minor: This depends on the degree of the future budget cuts to the program because this will affect the size of fees levied.

11. Major: The cumulative effect, especially with submission evaluation fees for new drugs or submissions involving extensive clinical evaluation will in some circumstances contribute to raising the barrier to entry for some new product ideas.

12. Major: The combined effect of phase 1, 2 and now 3 cost recovery programs will require our company to pay over $60,000 per year in fees. This has a very significant affect on our available finances. Fees associated with the marketing of drug products could cause us to keep many of our supplement products in the "food" category, where fees are not required.

14. Minor: In general, additional forms of taxation have a negative effect on competitiveness in a global environment that seeks low cost production and world class manufacture.

17. Major: These fees combined with the fees from Phase I and II of cost recovery have doubled the regulatory budget in our company.

18. Minor: These fees represent a very small proportion of total federal government fees we pay.

Overall, the fees impact on our business in that the cost of doing business is more expensive - the highest proportion of fees come from submission review fees. The establishment license fees will not significantly impact on fees we already pay since they are so small in relation to the total (in total we pay approximately $1,000,000 per year).

21. *Prohibitive: Because we pay taxes for services, now we have to pay again to get services we already paid for.*

22. *Major: The indirect effect will be that either illegal fabricators or veterinarians and pharmacists who dispense compounds and are not subject to GMP requirements and fees will become more attractive to price sensitive customers. There by reducing the demand for products manufactured by licensed establishments. In aggregate cost recovery will reduce our ability to be price competitive and reduce the number of product alternatives in the Canadian market.*

23. *Minor: Fees for the "Authority to Sell Drugs" and "Drug Evaluation" together with this new fee will begin to have an affect on our company. These are all relatively small amounts, but together, will add up to a substantial total.*

DESIGN ISSUES

Are the requirements of the proposed GMP and establishment licensing regulations consistent with your current business practices? (eg. are you already complying with GMP or ISO requirements) Yes__23___ No_0___

1. No: Some exception comply to US GMPs.

3. Yes: As was stated previously, compliance with GMP is very difficult as an importer without international harmonization. It is very difficult to convince an offshore supplier to comply with more stringent GMP's (generally) when their domestic market is one order of magnitude greater than their foreign market.

6. Yes: We comply with the GMP and are an ISO registered company.

10. Yes: We already comply with GMP. More details are required as to what information will be required in an ELA. Guidance is also required for information respecting: amendments, annual updates, etc.? (What has to be submitted for approval prior to implementation, vs. what can be notified in an annual report?)

12. Yes: To a great extent, however additional changes will have to be made to comply with the new revision of GMP Guidelines proposed (validation requirements, etc.)

15. Yes: We meet GMP and ensure products imported meet GMP. Establishment Licences is a new administrative burden used to obtain fee for service. A more harmonized approach for service fees will reduce the cost of administration by business and HPB

18. We are currently complying with GMP requirements.

19. It depends on how the GMP is applied to our business as some of the conditions seem related only to manufacturers yet if applied to us could have serious impact (ie: storage requirements, assurance of drug specifications, etc.)

25. Yes: As far as we are concerned, the current GMPs are in compliance. The annual licensing is an unnecessary extra burden being put on the HPB and on the Industry.

26. Yes: Except: Point 11 guidelines for GMP see penicillin issue.

What are the specific source of any problems you may have with the proposals (both the GMP and EL regulations and the proposed fees):
Lack of clarity/certainty Yes__22___ No__2___

1. Yes: The case of multiple corporate entities under the same management and under one roof needs clarification.

2. *Yes: Since I attended the workshop, and received the additional clarifying communications, I believe I understand how to calculate the fee. However, the instructions with the form to calculate the fee needs some expansion.*

4. *There is a lack of certainty that the proposed licensing scheme will confer any real value to GMP compliant firms. Compliant manufacturers will be subsidizing the costs of surveillance and enforcement for noncompliant firms without realizing any direct benefit. The costs to compliant firms are not going to be offset by the utility of the license for several years if at all. Indirect benefits will be realized by larger firms only through the forced consolidation of the marketplace. Reduced competition will ultimately cost consumers more. If Health Canada is serious about creating an environment where risks can be managed, the Act and Regulations will require complete revision to allow selective surveillance and enforcement of regulatory requirements. The present regulatory proposal does not consider the depth or frequency of inspection as being the most effective means available to manage risks presented by the manufacture of various drug products.*

5. *Guidelines for preparation of the Site Reference File need to be issued. The regulation is very vague.*

6. *Yes: No information is provided on the issuance times or inspections frequencies. Section C.02.022 and section C.02.023 have a provisional clause which is not explained "unless otherwise specified in the person's licence." There is no explanation how these provisions could be achieved. Above also applies to revised section C.02.025.*

7. *i) It is very difficult to assess the amount of fees to be levied based on the document. Only after thorough discussion with Drugs Directorate were we able to assess the fees to be levied. Simpler language and more examples could be used.*

ii) It is very difficult to interpret how we classify some of our products in the fee schedule. In the specific case of Vaccines, we import and package them at the (city) site. Since we are charged $10,000 under the Analysis Component of Biologic for a Fabricator/Packager we did not double count this charge on the import/distributor. If this is not how Health Canada views the classification of Vaccines in this situation, we disagree with the fact that we should be charged twice without any increase in activity. This would be an overcharge and is not within the spirit of the Cost Recovery - Establishment Licensing regulations.

8. *A greater number of examples need to be provided to allow the determination of fees to be fully understood.*

10. *Block 1 & 2 proposed fees form requires a guidance document since it is very hard to interprets what is being requested. Block 2 Importer/Distributor: (a) If you are a licensed fabricator in Canada and also importing products from Foreign Fabricators, you should not be required to pay an additional Domestic GMP inspection fee as this is already being paid in Block 1. No additional Facilities are required for the imported product(s). (b) If the Foreign Fabricator is licensed in Canada, there should be no need for the domestic importer to pay another analysis fee component as this would already be*

paid by the licensed Fabricator. In cases were the Foreign Fabricator is NOT licensed in Canada, then it would be appropriate for the importer to pay the analysis component.

11. Yes: - Not certain if I can direct ship from a US distribution centre to a Canadian customer (interpretation of C.02.018 and C.02.019 as revised).
- Not sure what C.01A.012 means re a "Country or association of countries./Meeting Canadian Standards" or how to reinterpret the GMP's for such a designated country.
- Does C.01A.009(2)B allow a company to avoid the requirement for authorized foreign facility for OTC drugs and hence avoid the fees for foreign supplier foreign reports evaluations? If so would doing so be a good strategy or will advantages associated with HPB administrative practice around MRA aspects cause me to seek authorized foreign facility status and hence pay the fees?
- Does the fee for foreign report evaluations only apply to foreign Government reports or to Company audits when presented in lieu of Government reports as in C.01A.009(2)B?

12. Yes: The present proposal requires double fees to be paid by companies (such as ours) that are both manufacturers and importers. The basic GMP fee should not apply twice, or to create an equitable program, should be a flat rate of $2500 regardless of status. The fees associated with foreign suppliers in MRA countries is presently to high - fees should be bases on HPB effort, which would be minimal in this case.

14. Yes: 1. Effectively another form of business taxation. 2. Unclear if the options to document evidence of GMP compliance are also changing for the purposes of preclearance of Drug Submissions. 3. Unclear what the specific requirements for Site Reference Files will be(ie) need for a guidelines document.

15: Yes: l. MRAs are not in place for implementing establishment licence 2. Site Master File templates describing the level of detail is not in place. The document is not harmonized with other agencies. 3. The amount of notice given is insufficient for budgeting the added cost to business preparing SMF and ensuring we can access a GMP inspection report from foreign markets, and ensuring staff availability to prepare documents. 4. The priority system for GMP inspection frequency is not clarified.

17. Yes: The guidelines have not been presented, only vague statements that the data required would be less than is currently required. Our concern is the amount of data which we will have to have available in Canada for inspection and our ability to convince our parent company to duplicate this data for Canada only.

18. 1. The administration of the licensing scheme at HPB is unclear, for example, which Drugs Programme Department(s) will be involved and what will the interactions between departments be?; will there be a separate group of qualified auditors to perform foreign facility inspections? 2. What are the ramifications if a wholesaler does not obtain a license?- how does this affect their suppliers and the distribution chain? 3. Regarding the requirement for notification and possible approval if there are changes to buildings, equipment, practices, procedures, personnel- the administration of this is unclear and may have significant impact on us:

- *how will the significance of the change be determined?*
- *which branch of HPB receives and reviews the changes?*
- *if approval is required, how is this determined and what sort of service can be expected to preclude delays in making the change.*
- *what is the length of time between submission and approval of a license amendment?*

4. *Definition of Manufacture- where does an off-site contracted distribution centre fit into the licensing scheme? 5. Regarding the Application for License (C.01A.004)- there is reference to submission of "evidence" and "data" establishing compliance to Divisions 2-4- it is unclear at this time what type of information is required. What are HPB's expectations? 6. Regarding the change to Regulation C.02.023(1)&(2) pertaining to product quality complaint handling, the term "producer" has been added. This should be made clearer by using or adding the term "manufacturer" or "distributor" 7. Regarding the Site Reference File, the expectations of the content are not clear. A guideline is required to facilitate the preparation of the file*

19. *Yes: As mentioned above, we do not have a clear idea of the proposed site licensing requirements, and/or procedures to inspect facilities.*

21. *Yes: Having subsidiaries located in the same building as us, we do not know how to interpret the fees structure.*

22. *Yes: No ability to predetermine cost of inspection.*

23. *Yes: Not everything has been clarified to my satisfaction:*
    - *fee structure (incl. the fee calculation for "dosage form classes")*
    - *why are the dosage form classes split up the way they are?*
    - *exactly what options do we have to verify compliance for foreign sites?*
    - *where are the guidelines for completing the Site Reference File?*

24. *Yes: Not enough importance was given to testing laboratories. This is definitely an error.*

25. *Yes: It has been suggested that under the current system the GMPs are applied inconsistently from province to province. We do not believe that it had anything to do with the regulatory authority of the HPB. Only the uniform application of the same rules was never a priority for the HPB. We do not see any new ways of enforcing the GMPs in the proposed licensing system that will change how they are applied uniformly.*

The problems are associated with the additional system of licensing which will create unnecessary burden.

26. *Yes: GMP guidelines. Requirement for separate building to fabricate penicillin products for veterinary use.*

Complexity Yes__10___ No__14___

1. *Yes: More in the presentation than per se.*

8.- Many of the definitions are still not understood and this further creates confusion.

10. Yes: Unduly complex, needs a guidance document.

11. Yes: C.02.012© appears to be requiring not only the importer but also the wholesaler to have a system to inspect the fabricator/packager. Surely this is an error regarding the wholesaler.

14. No : As expressed previously, there is a need for more adequate explanation through a wider variety of examples.

15. Yes: Additional administrative burden.

18. There appear to be a number of areas which will add unnecessary bureaucracy to the system- eg notification of changes which may or may not require approval (ie HPB becoming part of a company's change control process)

Fairness/Equity? Yes__11___ No___11__

3. Yes: The rationale of EL regulations from an importers perspective. As far as we are concerned none of this is necessary, it is nothing more than a cash grab.

4. There should not be a separate and additional base charge for fabricators who also import drugs in final dosage form.

5. Veterinary pharmaceutical companies have not been as regulated in the past as human due to lack of resources. This amendment may make all pharmaceutical companies equally regulated. Maybe they don't need to be.

6. Yes: Major pharmaceutical manufacturers are categorized as higher risk however, it is the "fly-by-night" operations which are really the high risk companies.

8.- Manufacturers with numerous 3rd party and / or foreign manufacturing sites may face greater financial complexity and cost than competitors who operate solely from one site.

10. Yes: If the foreign fabricator holds Canadian license then the importer should not have to pay an additional Foreign GMP Inspection fee or Analysis Fee: then the requirement to pay these under both Fabricator and Importer constitutes "double dipping". This is especially true with Biologics Fabricators which are required to be licensed. An option should be identified on the form if: I) The foreign fabricator holds a Canadian license then the importer should pay an Analysis Fee or Foreign GMP inspection fee; ii) if the importer is a Canadian licensed Fabricator, then they should not be required to pay an additional domestic GMP inspection Fee under Block 2. To do so would constitute a double payment.

11. No: An importer receiving several drug classes from a few plants will pay substantially less than an importer receiving the same products from many plants because of the $1250 flat rate for each foreign inspection report review. The cost of reviewing each inspection report seems excessive and there should be a reasonable upper limit or declining scale for report and reviewing from multi-site importers. As an importer using many sites my fees for reviewing foreign reports are approaching 70% of my total importer fees.

12. Yes: Cost recovery in general should be based on the relative amount of available resources the HPB must dedicate to a particular segment of the industry. The high degree of product safety and lack of technical complexity associated with the nutritional supplements segment makes it a very low risk and resource drain on the HPB. Therefore, we should not have to pay for the same degree of regulatory control that is required by allopathic OTC products. There should be a sliding scale of costs based on risk (greater than in the proposed program). Also, fees should be based on the effort required by HPB to perform an audit. As with annual product licensing, low product or category sales should result in a dramatically lower fee. Also, if a company is both a manufacturer and an importer, they are being charged twice for basic GMP and analytical requirements - this is not fair. This needs to be adjusted to a single charge.

14. No: 1. Canada's major trading partner does not have a similar fee. 2. The additional costs of auditing non-compliant companies will now be increasingly borne by those who have a history of ongoing compliance.

18. 1. It appears that a domestic manufacturer would be disadvantaged from a fee standpoint if an importer has supplier's assessed through an MOU or MRA (ie the fee for this type of assessment is less than the fee paid if manufactured in Canada). This is of concern since it does not promote domestic manufacturing and the subsequent positive impacts of this on the Canadian economy. 2. It appears that a domestic manufacturer would also be disadvantaged from a licensing application and maintenance standpoint in that changes must be sent to HPB for possible approval. This does not appear to be the case if the manufacturing is done outside of the country. 3. Regarding suspensions and the appeal process, a company's appeal to the Minister can take up to 45 days to be heard after receipt of notice by the Minister. This means that the company could potentially be under unwarranted suspension for 45 days. Potential price to pay for bureaucracy is too high in that the equivalent sales dollars over this 45 day period can be up to $45 million. This also poses a greater disadvantage to local manufacturers who are subject to a more rigorous GMP assessment under the proposed regulatory changes. 4. Regarding issuance of licenses and the minister being able to apply additional terms and conditions upon submission of a request, it appears that requirements may be delineated at various levels at HPB- ie presumably issues would have been delineated during the Drug Submission process so to add another level of review and possible additional requirements onto this would not be fair. This review process increases the possibility of receiving inconsistent requests at various levels of HPB (which is currently experienced now when different departments get involved with a similar issue) This applies particularly to local manufacturers who have a heavier compliance burden added. 5. Regarding the statement that licensing will provide a "level playing field", compliance and enforcement focus will

be based upon risk assessment and therefore it is not a truly level playing field, ie more latitude will be given to sectors deemed to be less of a health risk

22. *Yes: The proposed regulations and fees serve only to further regulate and already extensively regulated animal health industry while continuing to ignore the importation and use of unapproved veterinary drugs. The increased regulations will fuel the widespread underground market for pharmacologically active ingredients.*

23. *Yes: Are these proposals fair to importers and manufacturers alike?*

25. *Yes: On paper, there was always fairness and equity.*

Ability to comply? Yes___12__ No__10___

3. *Yes: See answer to first question in this section.*

8. *Greater resources will need to expended to track and maintain the Site Reference Files that will need to be created for inspection purposes.*

10. *We already comply with GMP and would be willing to pay fair and equitable establishment licensing fees.*

12. *Yes: The proposed fee schedule will have a large financial impact, as well as possibly forcing a rationalization effecting marketing and sales.*

23. *Yes: Will we be forced to use a different method of confirming foreign site compliance than is currently used (ie. self-inspection)?*

25. *Yes: The basic rules of GMP compliance are exactly the same as before. therefore, we will continue to meet the requirements.*

26. Yes: See penicillin issue.

Cost? Yes__10___ No__11___

1. *No: *Except for a minority of members*

3. *Yes: See cost calculations*

5. *Previously it was up to the importer to assess foreign manufacturers for GMP compliance and this assessment was reviewed during HPB inspections. Now we're expected to pay HPB to assess foreign manufacturers. This is an unnecessary cost.*

8. *Fees of this nature which will need to be paid annually will impact on our ability to fund head count increases, etc. especially with the new SRF requirements.*

10. Yes: Double payment required in the proposed regulations for importers (see above).

11. Yes: But manageable.

12. Yes: As mentioned above, the cost for the nutritional supplement segment of the industry is too high. Costs should be based on risk and relative resource requirements. As well, there should be a sliding scale to grade the fee based on category or product sales. Also, if a company is both a manufacturer and an importer, they are being charged twice for basic GMP and analytical requirements - this is not fair. This needs to be adjusted to a single charge. The charge for inspection fees to an importer from a MRA country is too high. The amount of HPB inspector effort to review compliance of a foreign MRA government inspection is very small - not worth the $1250 being charged.

14. Yes: Additional cost to industry has the potential to impact the overall cost of provision of safe and effective drugs to Canadians.

17. Yes: Although the fees are relatively small, the fact that their are fees creates a negative investment climate.

21. Erosion of our profitability

26. Yes: See penicillin issue

Other? Yes__6___ No__7___

3. Yes: Cost Recovery in general.

9. Yes: it further regulates an industry which is in compliance and totally ignores the major problems - illegal importation. It will make us even less competitive.

10. Yes: There is no information regarding the content of an establishment license application or amendments. The only other major Regulatory body requiring ELAs is the US, and they are currently considering combining the ELA into the Product License Application. Meanwhile Canada (at least for Biologics) is proposing the opposite. Harmonization would be good! Guidelines need to be issued ASAP outlining the information which will be required for submission of establishment licenses, amendment to existing ones and maintenance (what changes need to be reported and on what frequency, e.g. annual?)

20. Yes: Timing of implementation is too short.
Cost and timing of label change for Biologics. We have > 40 biological products and some are rarely manufactured.

Do the requirements of these proposals contradict or duplicate other obligations imposed on your business by:

Federal government? Yes___6__ No__17___

3. Yes: Yes, we already are paying taxes. This is no more than a tax grab to support a service that does not recognize the needs of our "natural products - herbs, homeopathic, supplement" market. These low risk products do not need such over-regulation.

12. Yes: Basic business taxes are being paid that are allocated within the government to pay for HPB resources.

15. Yes: The administrative burden of keeping products on the market is increasing through Annual Notification Establishment Licencing and in the future Drug Product Licencing. This will take effort away from filing by industry and review by the HPB of life saving new medicines for Canadians. The bureaucracy associated with operating a business in Canada could limit potential expansion of business in this area.

18. Terms and conditions appear to duplicate the Drug Approval process in some areas, ie it appears that there will be a regional review and a national review of amendments

22. Yes: Agricultural Canada establishment inspections

24. Yes: From the point of view that all testing labs should already be in compliance with GMP's.

Other levels of government? Yes__4___ No__19___

3. Yes, we already are paying taxes

4. Corporate levies are placed on (this company) at the provincial level.

8. Foreign sites may already have European or US manufacturing site reports. The need for a Canadian SRF may be redundant.

15. Yes: Provincial formularies are increasing the level of detail required in their applications. They are in effect reapproving products after a Notice of Compliance is obtained.

Other regulating bodies? Yes___2__ No__21___

3. Yes: We see this as escalating to "food products, cosmetics, etc. etc." We don't see the consumers in Canada demanding this extra "service", and demanding to pay for it either

15. Yes: FDA continues to do pre-approval inspections (PAI) for products manufactured in the US for the Canadian market. We must therefore prepare for two kinds of inspections namely HPB/GMP and FDA PAI. The effort spent amounts to the possibility of several weeks to months of government inspection. The effort is labour intensive taking away the ability to focus on product development and production.

International requirements? Yes__8___ No__14___

*1. Yes: * In the case of those complying with FDA regulations.*

3. Yes: Lack of harmonization with major trading partners.

4. (this company) is required to satisfy the GMP requirements of the international markets in which we sell. A long standing redundancy has existed in satisfying FDA and HPB concerns.

10. Biologics Fabricators are required to meet GMPs and have facility licenses by a number of other Regulatory bodies globally.

11. Yes: FDA GMP's and HPB GMP's are not absolutely harmonized regarding some of the details either as defined by the regulations or by respective administrative practice.

14. No : Concept of Site Reference File is new and potentially difficult to deal with in the situation of ex-Canada suppliers. Admittedly, the situation with EU countries will be somewhat easier as a result of the site file approach in these countries.

15. Yes: Foreign sites must prepare a Canada content and format specific Site Master File and also prepare Site Master Files for their own regulatory authority.

17. Yes?: These requirements are closer than what currently exists in Canada to what is required internationally. The concern is that the requirements are not the same.

20. Yes: In the absence of an MRA there is a duplication of effort in auditing and testing.

23. Yes: US requirements for manufacturing drug products do not always agree with Canadian requirements. Foreign (US) sites are forced to do additional work (eg. extensive raw material testing) in order to comply with Canadian GMP standards.
Also, Canadian GMPs require duplicate testing after receiving a drug product into Canada.

25. Yes: Bilateral agreements between Canada and certain other countries should imply that the bottom line acceptance of a facility by another jurisdiction should be taken at face value. We do not see any merit in HPB reviewing those reports at a an extra annual cost to the manufacturer. It will be a duplication.

COSTS AND BENEFITS

	Initial Cost ($000)			Ongoing Annual Cost ($000)		
	Total	Average	% Tot.	Total	AverageT	% Tot.
Administrative costs	281	14	25%	201	10	17.7
Operating costs	212	11	19%	221	11	19%

Capital costs	100	5	8.9%	0	0	0%
Fees	414	21	37%	592	29.6	52%
Sales Revenue	100	5	8.9%	218	10.9	19%
Total	1,128	56		1,138	57	

Comments:

1. *Cost of implementing GMP with our manufacturers will be in the range of $600K to $2M (i.e. about $1,4M each). Savings will only accrue after.*

2. *The $ impact of proposed fees and regulatory changes will be relatively minor:*
Additional Costs:
-Licensing Fee $20,000/yr
-Preparing Site Reference File
(1 local, 4 foreign - 3 person months) 30,000
Reduced Costs:
-Elimination of Narcotic Inspection
(1 person week)2,000/2 years

3. *We are a low risk industry and don't need any of this*

4. *The costs shown are estimates for discussion purposes only. The capital investment is assessed on the need to repatriate manufacturing procedures in the event that the marketplace dynamic shifts towards fewer suppliers. Recent industry experience with the single window inspection approach has shown an increase in inspection time, not a decrease.*

8. *Admin. cost is ½ a head count. Salary benefits and associated costs.*

9. *We spent significant time and energy on the BIT for cost recovery of evaluation fees. Industry comments were ignored or disregarded. Fees are in place and service standards are worse (Review times). This is even more pointless.*

11. *With direct shipment a ballpark estimate would be a net $3 million cost reduction which would be available for further investment in advertising/price reduction/volume growth, etc. Beyond this rough estimate, I cannot go without a more detailed plan. Certainly there will be some early stage manpower costs, systems design work, etc. Without direct shipment I see this as essentially an additional tax equivalent to the establishment fees to be paid and an administrative burden regarding additional submissions, plant profiles, etc. A rough estimate would be, say 2 people & fees = $150,000.*

12. *Primary expense will be to perform required audits of foreign suppliers.*

13. *Cost would be incremental and not substantial in these areas of administration.*

14. 1. Inspection timing not impacted 2. Initial implementation costs related to Site Reference File preparation and negotiation activities related to foreign suppliers. 3. Ongoing expense involves supplies and salary/benefits associated with a projected headcount increase of 1 to control/maintain compliance and manage change control activities related to the programme of Establishment Licensing/Fees.

18. Costs that will be incurred are for the most part unknown. In the absence of detailed requirements, the cost cannot be estimated. There will not be any savings (eg we will not benefit from the single window approach) and there will likely be a cost increase in many areas.

19. This analysis is impossible to carry out without more details as to how and what will be included in the licensing process

*21. * Total estimated losses ~ $200,000.00*

24. The financial impact on our company is minimal. The cost of an inspection will not be increased or decreased as far as we are concerned. Any differences, advantage or disadvantage, will be so small as to be insignificant.

PERSONNEL

Where possible, please estimate net impact on personnel requirements:

	Impact on Full Time employees		Impact on Part Time employees		Contract
	PY	$000	PY	$000	$000
Management	0.1	30	0	0	0
Administrative	2.0	211	0	0	0
Operational	4	145	0	0	0

Comments:

1. *It is estimated 50% of the costs associated with implementing GMPs and 85% of those associated with ongoing compliance will be personnel costs.*

2. *The impact is not measurable.*

3. *How can we tell yet?*

4. *An estimated 3 additional full time employee would be required should (this company) need to repatriate manufacturing capacity. The additional workload associated with the preparation and maintenance of the site reference files will be integrated within the present workload.*

7. *To ensure fairness and equity, it is imperative that the fees are charged based on the level of activity consumed by the Company and not charged (overcharged) based on a fee schedule that does not reflect the true activity level.*

8. *May not affect head count but will create great need to maintain SRF, etc. on a yearly basis and the need to estimate the yearly ELFs for the company overall.*

9. *We spent significant time and energy on the BIT for cost recovery of evaluation fees. Industry comments were ignored or disregarded. Fees are in place and service standards are worse (Review times). This is even more pointless.*

11. *It is beyond my ability to estimate this other than directionally. Assuming that direct ship is permitted there will be a reduction in the size of the Canadian distribution network. This will in part be offset by greater use of advertising resources (which do have a personnel component) as well as increased volume which will increase use of the remaining distribution network as well as customer workload. Reductions in laboratory staff will be offset at least in part by increases in quality assurance and regulatory staff to handle increasing submissions to HPB and supplier systems validation, monitoring and control.*

12. Primarily associated with audits of foreign suppliers.

13. Minimal impact.

14. Contract expense is for start-up activities which are estimated to be heavy to satisfy compliance requirements in first year of implementation and is for year 1 activity only.

15. Preparation of establishment licence will take:
- 1 fulltime regulatory person to prepare forms: 10 working days
- 1 fulltime administrative person: 5 working days
- 1 manager to prepare budget: 2 working days
- 1 finance person to review: 1 working day
- 1 material management person: 2 working days
to confirm site detail

18. It is estimated that this would be a minimum of $20,000, however could increase significantly. The cost impact cannot be assessed on loss of business, potential capital cost, loss of flexibility, cost of liability.

23. No impact

24. Again, we don't see any significant impact.

25. It is difficult to estimate the total cost in person years which will depend upon decisions regarding closing of certain facilities. As mentioned earlier, the out of pocket cost will be $ 20,000 per annum.

SUMMARY AND ALTERNATIVES

In summary, will these proposed GMP and establishment licensing regulations place your business company in a more, less or equally advantageous position in relation to your competition:

Within Canada?	More__2___	Less___8___	Equal__14___
In other countries?	More__2___	Less___12___	Equal__7___

1. **On average, should be equal. However, as pointed out certain members will see their position deteriorate. As for other countries, what is gained in reputation and notoriety will not be enough to overcome increased costs.*

3. *Less: In Canada less, because we are competing with large companies who have one plant which manufacture all they do, and make huge runs. As a niche seller, we don't have the large runs to amortize all these huge costs over. In other countries, they have their own GMP's which may or may not match Canada's. Also their we are competing with huge run manufacturers the same way. Your are treating us as "pharmaceutical" manufacturers when in fact we are not!*

4. *Less: The added costs will be spread across all products regardless of domestic or export sales intent. Consequently, the prices in the international market will need to reflect the added costs.*

9. *Less: Certain of our competition is illegal. Given that none of the proposed changes deal with that problem, we are obviously at an even greater disadvantage.*

11. *Less: Competitors importing from fewer alternate facilities as sources would seem to have an advantage.*

12. *More in Canada: Within Canada, (this company) is in better compliance with required GMP Guidelines than the majority of our competition. Therefore, these new requirements will affect others more than us. This new initiative will go a long way in enforcing a "level playing field" that should prove beneficial to (this company).*

Less in other countries: Externally, the cost of Canadian manufactured products will be relatively higher than other countries due to the increasing volume of additional Canadian taxes we are forced to pay.

14. *More/less: Depending on the Establishment Licensing requirement in a given jurisdiction, the competitive situation could be more or less advantageous.*

15: *Less: The ability to import product from foreign sources is now limited. Previously Canadian industry was able to obtain product from any source meeting. Canadian GMP based on either a Plant Mater File, corporate audit report, Canadian GMP foreign inspection or a foreign GMP report. This puts the liability of importing a product appropriately in industry hands and allows greater access to foreign sources. The current plan provides access to a limited number of countries with which we have a*

MOU to obtain inspection reports. The plan for recognition of foreign GMP through MRAs with the US, EU and Japan and possible agreements with NAFTA and Asia Pacific Rim is not in place. It is clear that EL under the current plans is not sufficiently developed to make it useful to industry. Once MRAs are in place however, we will be in a better position to compete for manufacture for world markets.

For local needs our access to contract laboratories, wholesalers and distributors will be limited to those willing and able to pay the fee. The risk of closing smaller Canadian business is increased. The EL fees appear higher in Canada than other countries and could limit continued manufacture in Canada.

18. Less in other countries: With local site there is more opportunity for HPB intervention (eg change control approval, potential for suspension due to inspection process). Process for foreign assessment based upon MOU is less expensive.

The ability to export may be affected. There is a potential for a positive impact only if establishment licenses are highly regarded internationally.

19. Equal: It should not change competitiveness if applied across the board, unless firms withdraw from the industry due to non-compliance. We do not operate in other countries.

21. Less: Because of the size of our company and the type of business, we are involved in (custom manufacturing), we will probably have to pay fees equal to those paid by companies who have gross sales 20 times ours.

22. Less: The underground market for animal health pharmaceuticals will grow substantially, weakening our competitive position.

24. Less: Because of the way the licensing is being handled. All testing labs, even those that are not compliant will be licensed. This is wrong!!!

26. Less (both): Competition of unregulated bulk chemical importers for veterinary use.
US and E.E.C. countries see comments under harmonization.

Do you feel that this initiative will achieve Health Canada's objective of providing a uniform, consistent and risk based approach to establishment licensing in Canada?
Yes__12___ No_12____

4. The Food and Drugs Act and Regulations were conceived in an era of absolute risk avoidance. However, current risk management practices necessitate selectively surveilling and enforcing compliance where the risks are the greatest. The present Act does not accommodate these objectives easily. The efforts of the Drugs Directorate to adapt the Food and Drugs Act and Regulations to address the current health and fiscal environments are analogous with conducting delicate surgery with a truncheon. Compliant manufacturers exercise good manufacturing practices, regardless of legislation, to minimize product liability and to enhance quality as a competitive tool. Concern with noncompliance is less immediate to a manufacturer than concern with

potential liability and loss of profitability. Literature suggests that the frequency of inspection is the greatest motivator for compliance amongst noncompliant firms and is only effective in accomplishing compliance if the inspection frequency does not exceed 3 years. Manufactures with a history of compliance stay compliant without intensive government surveillance because integrating GMPs in the culture of the organization is the most cost effective means of minimizing product liability and maintaining product quality and consistency. Company vitality and profitability stems from being consistently able to enter markets with high quality products manufactured under consistent conditions. The most effective way to manage risks associated with GMP noncompliant firms is through more intensive market surveillance not, through regularly and habitually inspecting compliant firms. The value of a license is minimal to compliant firms. The international value of the license as currency is constrained by divergent political agendas and the absence of broad acceptance by our trading partners. The Drugs Directorate Inspection Strategy may be better served by developing mechanisms to defer the monitoring of compliant firms to a separate body and concentrating on those firms who pose a greater risk to the public. Serious consideration should also be given to rewriting the Act and Regulations to reflect HC objectives amid current realities.

6: No: The higher risk companies are the smaller unknown manufacturers and importers. These companies are the ones which should have more frequent inspections rather than the larger reputable companies.

9. Yes: It probably will but, the practical end point is unchanged. Legitimate industry already complies or does its utmost to do so.

10. No: Not consistent, it penalizes Canadian licensed Fabricators by imposing unwarranted importation fees. It should NOT be a disincentive to Canadian manufacturing

11. No: Category IV drugs should have been charged in a lesser way than other OTC's to reflect substantially lower risk. Audits involving many sites with few products each provide a much more thorough (and expensive) review and greater benefit to risk reduction than audits involving few sites with many products and product types each.

12. No: For the reasons stated throughout this survey - especially for the nutritional supplements industry, primarily related to the "relative risk" issues.

14. Yes: While this approach to Establishment Licensing takes into consideration the relative risks associated with various classes/categories of drugs, it does not specifically address the risk data associated with history of compliance

15. Yes/no: The current system of GMP assessment applied a level of GMP inspection that was appropriate to the risk of the business, namely biologics, pharmaceuticals and radiopharmaceuticals although it was not harmonized. The only real change is that by changing the regulation that all businesses require an establishment licence, a fee can be levied. The fee for service is now an established reality.

For wholesalers, distributors, and laboratories, the risk to product quality was clearly on the company's shoulders. The company using these services under the current system must satisfy themselves that they will ensure product integrity or test according to acceptable practice. The new system of GMP inspection and the requirements of the establishment licence will shift the responsibility away from industry that imports product or uses external contract services (i.e. manufacture, package, test, distribute) back to government. The liability should stay with industry.

18. Current experience indicates HPB's lack of consistency in application of Regulations (by region, by industry sector) There is no confidence that this will change significantly in relation to the licensing initiative.

20. No: Inspection strategy insufficiently defined
Potential for confusion between process driven biologic product and pharmaceuticals
Potential for increased time in "case by case" (biologics/ prelicencing inspections)
Likely inefficient in X-Canada auditing

21. No: This is not the good way.

22. No: It serves only to further regulate an already extensively regulated animal health industry while continuing to ignore the importation and use of unapproved veterinary drugs.

24. No: Not for a long time yet and not as long as important decisions are made without the consultation of testing labs from the very beginning. Bring in testing labs as an afterthought is not the best way to deal with such an important situation.

25. No: The application of uniform GMP rules was never accomplished before, why would it be any different now. The legislative authority does not change.

26. Yes: Qualified on the basis of our concerns relative to the veterinary market.

Do you feel Health Canada's objectives could be better achieved through:
Greater harmonization (if so, how) Yes__18___ No__4___

2. This will eliminate unnecessary duplication of both government and industry costs. There must be vigorous effort to quickly establish Mutual Recognition agreements and Memoranda of Understanding.

3. The bottom line here is don't bother us with any of these fees until you achieve harmonized GMP's with all of our major trading partners. Until you do, forget these fees

4. Global harmonization will result in greater benefit to Canadian manufacturers and Public than to the government bureaucracy. Health Canada's objectives will be met if the public is afforded a greater choice of safe, high quality drugs. The choice will be effected by decreasing the regulatory burden on manufactures and stimulating business.

Harmonization of the GMP requirements globally should be accompanied by harmonized surveillance and enforcement approaches.

8. Plan for a European MRA is underway but one with the US would be of more benefit and impact.

10. Yes: Detailed requirements for applications for licenses or amendments to existing ones (Biologics) are not available; Therefore we can't comment on the degree (if any) of harmonization achieved.

Regarding extension of licensing requirements to other sectors (Biologics & Radiopharmaceuticals have always required licenses) appear to be consistent with a number of other countries.

11. Yes: The HPB concept of GMP and the FDA concept of GMP are very similar differing only in a few details. Yet the devil is in the detail. When a company tries to harmonize and satisfy both, it must either take the most conservative course (with cost implications to all North America) or run the risks associated with the complexities of running two systems. Canada should fully and unconditionally accept US cGMP's from US plants. US should fully and unconditionally accept Canadian GMP's from Canadian plants.

12. Yes: In the nutritional supplements industry, many other countries treat these products separately from pharmaceutical drug products. Their premise is, and Canada's should be, that these products pose a far greater margin of safety and, therefore, require less government effort and fewer resources to control. Since cost recovery should be applied based on the r ıtive cost associated with specific products, fees for manufacturers of nutritional supplements should be less than allopathic medicines.

14. Yes: 1.Recognition of complementary GMP systems to supplement an existing system as a basis for compliance would seem to be a more progressive approach than building, or rationalizing(developing a funding basis for support) a separate infrastructure.

2. There is no doubt that the MRA system of compliance validation and assurance is the desired end and this initiative requires directed focus and expedition in terms of resource deployment recognizing its progress to completion is directly proportional to the will of the parties involved.

15. Yes: The development of MRAs for GMP is positive for Canadian manufacturers. This will allow greater recognition by other markets that we meet their GMP requirements. This will allow us to bid for manufacture of products for world markets. The ability to compete in world markets should help factories expand business and keep from closing. Continued efforts to harmonize GMP requirements globally will put Canada in a better competitive situation, especially with the US market.

The Site Reference File (SRF) is another Canada specific document. The information requirements should be harmonized with countries with which we achieve a MRA. The work of preparing such a document for every building we use is an additional burden to industry. We believe the SMF will not reduce the GMP inspection. The level of detail (which has not been clearly defined) is less than the current Plant Master File.

17. No: This depends on the specific data required to be submitted and will depend on how the guidelines are written.

18. Through provincial/federal harmonization initiatives. Through more focused effort in expediting MRA and MOU initiatives.

20. Yes: External MRA. Internal Training and accreditation of inspection

21. Yes: It will help us for exports.

22. Yes: The proposed regulatory amendments should harmonize with the US Food, Drug, and Cosmetic Act relative to the importation of active ingredients.

23. Yes: Harmonization (and an MRA) with the US would be helpful in streamlining the compliance requirement for those that import from the US

25. Yes: If you HPB will accept the GMP reports of other countries without wasting further time and effort on reviewing them annually at our expense, harmonization will be useful. But that does seem to be the proposed intent.

26. Yes: In terms of the veterinary field, it is a resounding yes. The US is about to undertake consultations to develop separate veterinary drug guidelines. Already FDA regulations clearly place Canada at a disadvantage in terms of control over illegal import and use of active pharmaceutical ingredients (API's).

Alternative regulatory approaches Yes__12__ No__10__

3. Yes: You can set up a classification for the products sold in our Industry which recognizes the low risk associated with these products. A separate DIN system, a separate set of GMP's which is consistent with our major trading partners for these type of products. Then we can be competitive in the world and at home.

4. For firms with a history of compliance with the GMP requirements the Drugs Directorate should consider accepting the results of corporate inspections. Corporate inspectors could be accredited by Health Canada and requirements to maintain accreditation developed and written into regulation. The Drugs Directorate could then concentrate on delinquent or start-up firms. The approach of involving industry as inspectors for the purpose of achieving federal objectives has been instituted by the federal regulators responsible for weights and measures and operated with success. The authority to designate inspectors is vested with the Minister of Health and not limited to federal employees

5. Put more responsibility on the importers to assess foreign manufacturers.
If a firm has a history of compliance, issue a 2 year licence.
Issue 2 year licences to firms who are only wholesalers.

Issue 2 year licences to manufacturers dealing with non-prescription drugs and Veterinary drugs.

8. Need for elimination of a SRFs.

9. No: Address the main problem of illegal activity within the veterinary market by making it a criminal act to import/sell non registered products in Canada.

11. Yes: Full blanket recognition of US cGMP's, and others as appropriate, consistent with the full blanket approach of Canadian F&D Act Schedule "B" acceptance of USP & various other pharmacopoeia or child resistant packaging standards similar to Schedule 800 of Canada Gazette Part 1 June 10, 1995. It is noted that the US cGMP's already appear in the USP which is recognized in Schedule B to the Food and Drugs Act.

12. Yes: As mentioned above, separate categories (even if within the drugs directorate) for nutritional supplements would provide for a more equitable allocation of resources and, therefore, fees to be recovered. Another way to fairly allocate fees to be recovered, based on relative risk (and therefore the amount of government resources required) could be to develop a compliance rating system. This way companies could be graded according to their peers in their specific market segment, eg. nutritional supplement manufacturers. Fees could be decreased based on good performance (similar to car insurance discounts). Fees should be based on relative level of required government resources. Clearly, companies requiring assistance in achieving GMP compliance, or marketing products in higher risk categories, will require more government resources - they should pay more than low risk, high compliance companies.

15. Yes: The GMP inspection information requirements should be broadened to include corporate audits and Plant Master Files (PMF). The HPB believe there is inappropriate detail in a PMF. The detail in a PMF should be reviewed and modified if needed.
The EL process should be harmonized with the annual notification process. By requiring filing of these two documents at different times of the year, the administrative burden of maintaining products will take away from New Chemical Entities which add to Canada's Health care needs.

18. Yes: The current program of abbreviated inspections and periodic full inspection appears to be more efficient and more cost effective for HPB than would be imposed by the licensing scheme.

20. Yes: Greater reliance on self inspection.
Increased change control and decreased testing.

21. Yes: Targeted inspections with clear objectives.

22. Yes: Separate veterinary pharmaceutical guidelines.
Greater penalties for violators of the Food and Drug Act.
More clarity in the regulations for Veterinarians and Pharmacists who compound drugs for

resale. Currently numerous pharmacists and practitioners fabricate drugs for general resale and are exempt from regulation under the pretense that their fabrication is for a given patient as outlined in the regulations.

24. No. More rigorous & competent regulatory approach.

26. Yes: Separate guidelines for the veterinary field are an absolute must. The Food & Drug Act must also recognize active pharmaceutical ingredients in addition to drugs in dosage form.

Alternative non-regulatory approaches Yes__2___ No___15__

1. Adopting ISO standards could be a better alternative.

4. Good manufacturing practice compliance and enforcement is one of the few areas where the requirements and compliance program need to be codified.

11. Yes: The HPB if not willing to accept US cGMP's which includes US regulation, guidelines, podium policy, differences, etc., could help in a big way. Develop a list of differences from US cGMP's that HPB sees as significant. Allow importers the luxury of verifying that their US sources are in compliance with FDA plus the HPB's Canadian list of differences. HPB would be are more adept at knowing the critical differences that count than any individual company. By surfacing the differences, HPB could decide to eliminate some, perhaps all of them. Canadian regulatory personnel would be more able to work with US regulatory personnel to educate US operations. Currently we need to stay abreast of the dynamics of BOTH FDA and HPB regulations and administrative practices to spot and deal with emerging differences to ensure Canadian compliance. If we could focus on staying current with an evolving HPB list of differences rather than as individual companies trying to define the list it would be more efficient and effective and provide a better basis for a level playing field from company to company..

14. No: Understanding what approach is affordable within the budget constraints and mandate of the Agency is key. This analysis is necessary versus an approach that uses as its basis of development that it is necessary to raise funds through a form of taxation for an existing system's support, be it good, bad or indifferent.

18. Yes: HPB should be expending resources in areas which are least regulated and most non-compliant. They should be funding this through cost recovery. Additional requirements to compliant firms should not be added.

In summary what are your key concerns (i.e. cost, fairness, equity, effect on competitiveness, etc)

1. Concern number one : this fee proposal (as was the case with phase II) puts a much greater burden on smaller companies than on larger ones. Already, Canadian manufacturing operations are perceived as being much less (+20%) competitive than their US counterparts. The combined effect of GMP and EL fees will not contribute to redress this situation. On the other hand, GMPs are unavoidable and most members will strive for FDA approval. Concern number two : within our group, these proposals will have detrimental effects (even prohibitive) on some members. Not certain that relief is available.

2. Once the validity of Cost Recovery is accepted, the proposed approach appears to be appropriate.
The financial impact is not onerous.
The fees attempt to be activity based and thereby fair.
The impact on competitiveness is minor to neutral.

3. As I've said all through this Impact Test, the products we sell are Not pharmaceuticals, and we should not be regulated and treated as pharmaceuticals. (And I don't care what the Food and Drug Act says is a drug - it was written at a time when the products sold in our Industry were not an issue.) Canadians want the products that we sell, or we would not be selling them, and if we cannot sell these products, then they will either be sold through the underground, by mail order from the US, or by people driving there and buying there. Either way, jobs will be exported. Be aware that if this happens, we will be very vocal as an Industry, and the public and politicians will hear all about it. There is already a very high level of frustration and the paternal attitude of HPB, and the amount of products not allowed in Canada except by mail order or personal shopping out of the country that are sold in most other countries of the world. Cost recovery is bad for us, and Part III is really bad. Please do not proceed without major changes.

4. - Value of the license to compliant firms is dependent on the negotiation and approval of MRAs and MOUs. Without international utility, the underlying objective of the licensing program, i.e. financing the Health Canada drug inspection program could be better achieved through an alternate mechanism.
- Forced marketplace consolidation. The costs of licensing and compliance with the new GMP regulations could necessitate repatriating manufacturing capacity from smaller specialty partners.
- Disproportionate hardship on manufacturers who fabricate and import drug products. The present structure favours establishments who are single purpose. The right to import should be conferred on the fabricators since by virtue of being fabricators necessary infrastructure to import is already in place. Additionally, the single window inspection approach suggests that all phases of the operation will be assessed for compliance. The separate base fee for firms that also import cannot be justified.

5. We are a Canadian company and do not have the cash flow of the large multinationals. The fees will have to come from reducing budgets for other departments or increased selling prices.

6. Although the cost recovery will be equitable to all manufacturers there appears to be no incentive to expand the Canadian manufacturing base.

8. Cost to fees and impact on other resources, e.g. effect on personnel resources.

7. To ensure fairness and equity, it is imperative that the fees are charged based on the level of activity consumed by the Company and not charged (overcharged) based on a fee schedule that does not reflect the true activity level.

9. Address the main problem of illegal activity within the veterinary market by making it a criminal act to import/sell non registered products in Canada.

10. If Canadian fabricators are licensed they should not pay an addition domestic GMP inspection fee if they also import. Foreign fabricator which have a Canadian licensed facility should not (or their importer should not) have to pay a foreign GMP inspection fee or analysis fee under Block and Importer. The definition of "building" must be consistent with clarification note of August 23, 1996 from A. Butterfield and the fee form should be edited to replace "Building" with "site" or "company".

11. Competitiveness, cost and fairness lie at the heart of the need to be able to import directly to customers. Systems can be deployed to assure full GMP compliance. If an importer is forced to receive a drug onto his premises (even validated drugs by current Regulation C.02.019, must be so received at least for identity testing) it puts waste and duplication into the distribution system and creates a non health related regulatory barrier to free trade, placing importers at a disadvantage to local manufacturers who are not forced to maintain additional distribution hubs, nor repeat I.D. testing. If the new wording of C.02.019 now removes that barrier fairness is restored.

Furthering harmonisation with the US and other advanced countries is important and will reduce risks through system simplification and uniform standards. Until full harmonization is achieved, it would be very beneficial to seek a uniform industry/HPB understanding and alignment as to where harmonization is lacking. This would focus uniform attention by companies on properly dealing with the items as well as direct attention toward elimination of the differences where appropriate.

I have probably overestimated costs by $6250 because the forms suggest independently counting my ethical import operation, also as a domestic packager. Also, we need a declining scale for audit report review for multi-site importers. Uncertain as to how the new requirements on wholesalers will affect my company.

12. - Key concerns include all of the examples stated, as explained throughout this survey. Additional fees imposed on manufacturers of nutritional supplements place an enormous financial strain on them that is not warranted. Fees should be based on relative risk, and required government resources to control each segment of the industry.
- There should not be an overlap of fees charged to companies that both manufacture and import products, ie. the basic GMP fee and analytical fee should not be charged twice. As well,

the fees associated with inspector review of government audit reports from MRA countries appears too high - this should be based on effort.

- While we support the fact that increasing GMP surveillance should help to ensure a consistent, high degree of product quality, the cost to achieve this to individual companies is extravagant.

- As well, continuing to levy fees on Canadian companies makes them increasingly uncompetitive in a global market. The number of closures of Canadian pharmaceutical plants over the past 5 - 10 years clearly shows that.

14. 1. Cost is not prohibitive.

2. Competitiveness versus the US on the basis of the approach there would seem to put Canada at a disadvantage relative to cost of this aspect of compliance.

3. Fees are formula driven and from that point of view represents a progressive tax and in that sense is equitable.

4. Need to define a practical phase-in period as the indicated January 1, 1997 date is only achievable from the point of view of fee assessment and collection. It is not practical to have all other aspects this initiative in place by the aforementioned date

15. 1. Added administrative burden with no added value in GMP inspection

2. Limiting the countries from which we can import products

3. Reducing the number of contractors in Canada to manufacture, package test or distribute centres if they are unable to pay establishment licence fee

4. Implementing a system of obtaining foreign GMP inspection reports when MRAs are not in place

5. The Site Master File is a Canada specific document. It is a contradiction to allow for MRAs of GMP inspection and then require a unique to Canada document.

6. The levy of several different fees for service is a nickel and dime approach causing more work for both industry and HPB to administer. This will make it very difficult to forecast budgets

16. It is felt that the effect on testing laboratories would be positive and allow for better control of the analyses performed.

It would also be extremely advantageous for marketing as the client would know that the laboratory is licensed to perform pharmaceutical testing.

17. The major concern is how the fees will be viewed by our parent company. The existence of fees could reduce the opportunities to attract investment to Canada. Secondly, the outline of the exact data requirements for the establishment licence is not included and therefore our ability to determine if this data is available in Canada is not possible.

18. 1. The licensing scheme was initially presented as cost recovery and appears to have turned into an escalation of regulatory requirements for companies.

2. Canada is currently viewed with respect internationally and we are able to sell internationally with our current GMP's and regulatory requirements. The imposition of further restrictions will hinder our ability to compete internationally and provide

economic development for Canada.

3. *This does not necessarily represent a level playing field in particular between local manufacturers and importers. For example, the requirement to notify HPB of changes provides them with the option to perform an inspection, thereby possibly imposing additional requirements. This type of change notification does not appear to be required for importers. It also appears that Canada is proposing to become more stringent than the USA regarding licensing of their local manufacturing facilities.*
4. *There will be added layers of bureaucracy with the new licensing scheme. For example, the two tiered approach to approval (regional and national) will add to the burden on a company. Any delays on the licensing side will offset gains in efficiency currently experienced on the submission approval side.*
5. *Appears that this could result in a significant cultural change in Canada regarding industry and HPB relations as HPB's compliance and enforcement mechanism is being strengthened. This could lead to a more adversarial relationship as has occurred in other international markets, eg USA. It could impose a move away from the historical position of encouraging voluntary compliance and allowing negotiation of alternate means of compliance. With the possible pre-approval of changes through inspection or otherwise, the trust and reliance on a firm's ability to voluntarily comply would no longer seem apparent. The strengthened enforcement could also result in a firm's inability to negotiate in the presence of a threat of a possible license suspension.*
6. *Based upon HPB's current structure and resources, it appears that they are not ready to support such a program starting January 1997. It is unlikely that the expectations of industry will be met. Although service standards have been discussed, certain programs are still under development at HPB (eg their quality assurance program aimed at ensuring consistent application by HPB across the country). Guidelines have also been promised (eg preparation of a site master file) which will facilitate industry's compliance with the program. It appears that such guidelines have yet to be initiated.*
7. *The affect that this process may have on our ability to adopt new technologies may be significant in particular if we must obtain approval prior to their implementation. HPB may present roadblocks due to uncertainty in application of the new technology to existing standards as well as a resistance to being the first Regulatory body to approve something new.*
8. *In the delay of the publication of the 4th edition of the GMP guidelines, it appears that there may be further changes considered from the original approach which provided consideration of such things as alternate means of compliance. It is necessary to understand what these potential changes may be to assess the overall impact.*
9. *Risk assessments should not be done in isolation of compliance history. There may be more risk associated with sectors that are not currently regulated or are non-compliant.*
10. *Since the fees are so closely linked with specific products, the Treasury date of implementation should be moved to October to coincide with the DIN fees connected to submission of the annual Drug Notification Form. It would be much easier for companies to coordinate payment of the fees if they occurred at the same time of the year*

19. *The key concern is obviously the unknown element of regulatory requirements, given one body we should have a clear indication of the impact and responsibility of wholesalers. Unfortunately we do not. Secondary is the speed of implementation which at this point*

appears so fast that we will not have answers until the GMP and licensing is already in place

20. Lack of harmonization within HPB and with other agencies.
Potential training and multidisciplinary expertise within the inspectors
Unreasonable Implementation time lines.
Greater administration burden on manufacturer.

21. As we commented when we completed the « Cost Recovery Analysis for Phase I », it is not equitable for a company who sell for $1 million dollars a year of a medication to pay $500.00 for a DIN when the neighbour company pays the same fee for a product having $25,000. per year of total sales. We are again this time facing an equivalent situation where small companies with gross sales figures 10 or 20 times lower than larger firms who will pay the same licence fees. This makes no economic or business sense, some are struggling with the fees already imposed. The new fees will signal their downfall.

22. Fairness, equity and competitiveness. Continues to allow pharmacists and veterinarians to mass produce drugs without being licensed.
Continues to allow veterinarians and pharmacists, producers and the general public to import pharmacologically active ingredients without license and control and utilize these ingredients in competition with fabricators required to be licensed and controlled under the Food and Drug Act.

23. Key concerns:
- timing: these proposals are being rushed through--will all the details be finalized by Jan/97?
- will self-inspections and internal audit reports be an acceptable way to confirm foreign site compliance?
- are Site Reference Files mandatory and when will we see the guidelines for preparing them?
- is the fee matrix fair to manufacturers and importers alike?
- how will non-licensed companies be dealt with?
- why is the dosage-form-class part of the fee matrix so elaborate and why so many dosage forms?

24. The lack of adequate enforcement, inspection and control of the industry. It is obvious that an important feature--testing, was given very little importance. Perhaps this is a reflection of how testing is viewed by the pharmaceutical industry. Materials of inferior quality are reaching the consumer and DD is failing miserably in its mission and responsibility and all this to the advantage of importers and manufacturers that are benefitting from infrequent and inadequate inspections.

25. The proposed objectives of this initiative are : 1. Improve efficiency of inspection and product analysis programme. 2. Uniform GMP and licensing framework. 3. A fee schedule. There does not appear to be anything new to improve the efficiency of the compliance system and uniform application of GMPs. We agree that the proposal will accomplish the last objective of the introduction of fees and creation of more paperwork for issuing the licenses.

26. *By themselves the GMP and establishment licensing regulations may seem acceptable. They do not however render a level playing field for the veterinary field. In fact they exacerbate our already unfair situation. Until the deficiencies in the government's ability to control the importation and sale of non-approved substances and unless there are separate manufacturing guidelines for veterinary products, our industry will not flourish and, in fact, will likely decline.*